

**A TEXT-BOOK OF
SURGICAL
PATHOLOGY**

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SURGICAL PATHOLOGY

CHAPTER I

INFLAMMATION

INJURY or infection insufficient at once to impair the vitality of tissues stimulates the reactive process known as inflammation. Since the effects of injuries and infections constitute a large part of a surgeon's work, the study of inflammation may justly be regarded as of fundamental importance to the surgeon pathologist.

Inflammation may be caused by a number of physical and chemical agencies, including physical trauma, irritation by foreign bodies, heat, cold, light, electricity, X-rays and radium. Inflammation may also be caused by pathogenic bacteria, and this is by far the most important type. Inflammation may be acute or chronic, according to the intensity and duration of action of the causative agent, and various degrees of both acute and chronic inflammation occur, according to the specific type of bacterium or trauma responsible.

The inflammatory reaction occurs as a response to the irritant effects of toxins secreted by the bacteria; or, in the case of aseptic inflammation, of the products of tissue breakdown at the site of injury. Generally, the changes in acute inflammation are concerned mainly with neutralizing, destroying and eliminating the causative agents, and they involve varying degrees of damage to the affected part. In chronic inflammation, on the other hand, whilst destructive changes are still apparent they are of a lesser degree, and are often merged in or obscured by changes of a reparative nature—the process of repair.

Acute inflammation, in its broadest sense, includes three distinct processes—the local vascular phenomena at the site of the lesion, the local reaction of the fixed tissue cells, and the constitutional effect characterized by leucocytosis and antibody formation.

The local vascular phenomena are responsible for those features of acute inflammation seen on clinical examination. The blood vessels become dilated and render the part red and hot; blood plasma exudes from the dilated vessels and causes swelling; the sensory nerves, irritated by toxic substances and perhaps compressed by œdema, give rise to pain; and finally muscles, joints and glands within the inflamed area suffer in varying degree impairment of function. Thus originate the five cardinal signs of inflammation—*rubor*, *calor*, *tumor*, *dolor* and *functio læsa*.

The first exact description of the vascular changes in acute inflammation we owe to Cohnheim, and it is no exaggeration to claim that his observations, as recorded in his *Lectures on General Pathology* in

1877, form the basis for our present knowledge of inflammation. Cohnheim's studies were mainly carried out upon the frog, and the most instructive are those in which he examined the microscopic changes in the vessels of the mesentery, in which inflammatory changes were induced by the application of weak acids.

The earliest change observed at a site of inflammation affects the smaller blood vessels, especially the smaller veins and capillaries. After an inconstant and transient constriction these vessels become dilated, sometimes to twice their ordinary size. Not only do the vessels dilate, but also innumerable capillaries which in the normal tissues have been empty, collapsed and unrecognizable, now become visibly distended with blood. The immediate result is a greatly accelerated blood flow through the affected part, but after a short time—rarely more than half an hour—a further change becomes apparent. Although the total blood flow through the part remains greatly increased—witness the local heat felt on examination—the flow through the individual vessels becomes reduced. Indeed, in severe cases the stasis is so marked that the individual blood cells can be recognized not only in the capillaries, but also in the veins and even, during diastole, in the smaller arterioles.

It seems probable that this slowing of the blood stream is attributable to two factors. The first is that the endothelial cells lining the vessels, normally of flattened character, at this stage are affected by the bacterial or other toxins and become swollen, so that they project into the lumen of the vessel and partly obstruct it. The second factor is that as a result of the escape of its fluid content into the tissues the blood now becomes more viscous and flows less freely.

Now appears one of the most striking phenomena in the whole process. In Cohnheim's words, "the eye of the observer hardly has time to catch all the details of the picture before it is fettered by a very unexpected occurrence." Usually this takes place in a vein, less often in a capillary, and it consists in the emigration of the leucocytes through the vessel wall into the tissue spaces.

Normally in the veins the blood cells tend to occupy the central or axial part of the stream, whilst the peripheral or plasmatic zone consists mainly of plasma with an occasional leucocyte. In inflammation, as the blood flow becomes sluggish, this disposition is lost, and the original plasmatic zone fills with innumerable leucocytes, which move slowly and unevenly, as though driven along by the blood flow and yet held by an adhesive quality on the part of the endothelium. Eventually the internal surface of the vein appears as though paved with an unbroken layer of leucocytes. Now begins the leucocytic emigration proper: it almost looks as though the leucocytes squeeze themselves through the vessel wall between intact endothelial cells, and gradually resume their original shape on reaching the perivascular tissue spaces. The minute gaps left after their passage appear to be repaired immediately the cells have escaped.

The migration of the leucocytes does not cease when they have left the vessels. Partly carried by the flow of plasma, partly attracted by chemotaxis, they are drawn towards the seat of inflammation. There

NATURE OF LEUCOCYTE RESPONSE

they secrete enzymes with bacteriolytic properties, they engulf organisms or minute foreign bodies, or they may themselves be destroyed by the bacterial or other toxins.

In the wake of the leucocytes, red blood cells also may escape from the vessels by the process of *diapedesis*. This is not a striking feature in the majority of inflammations, but occasionally it is conspicuous.

Keeping pace with the cellular migration, there occurs a transudation of plasma into the tissue spaces or on to the serous surfaces. This transudation is due partly to the toxic damage to the capillary and venous walls, which impairs the permeability of the endothelial membrane. It is also attributed to the fact that the tissue colloids, which are of low osmotic pressure, and are broken down by the bacterial or other toxins into crystalloid substances, which, being of relatively simple composition, exert a high osmotic pressure and consequently withdraw fluid from the vessels.

Escape of blood plasma is a potent factor in the defence against bacterial infections, for it not only dilutes the toxins but also exposes them to antibodies and supplies opsonins which facilitate phagocytosis.

In some circumstances, especially when poured out upon a serous surface, the fibrinogen-rich exudate becomes clotted, and this may have an additional value as a means of arresting mechanically the spread of an infection. This is seen most strikingly when an acute appendicular infection is circumscribed by fibrinous adhesions between the surrounding coils of intestine.

The Nature of the Leucocyte Response. One of the most remarkable features in the whole process of inflammation is the behaviour of the leucocytes, particularly, in acute infections, of the polymorphonuclear leucocyte.

Reference has already been made to the emigration of the leucocyte—how it settles to the periphery of the blood stream, ranges itself alongside the vessel wall, extrudes itself between the endothelial cells, and finally moves in the tissue spaces towards the focus of inflammation.

If the leucocyte now comes within range of any particulate matter—a minute foreign body or a bacterium—it may exhibit the phenomenon of phagocytosis (*φαγεῖν*—to eat). First the cytoplasm on the side nearest the particle bulges, and then projections or pseudopodia appear, which encircle the particle and draw it into the substance of the phagocyte. Within the cell the particle is subjected to the action of enzymes and digested or dissolved—or if it cannot be digested it may be discharged from the leucocyte and set free again in the tissue fluid.

It is interesting to note in passing that the property of phagocytosis, so beautifully seen *in vivo*, is entirely lost in *in vitro* experiments if the leucocytes are first washed in physiological saline. From this it is clear that some elements from the body fluids are required to facilitate phagocytosis. These elements are known as opsonins (*ὀψων*—a sauce). They are present in normal blood plasma, and are found in greatly increased amount in the plasma of patients whose immunity is raised in response to an infection.

The phenomenon of phagocytosis by leucocytes was discovered by

Metchnikoff almost by chance in the course of a general inquiry into the cellular responses to injury shown by the simpler forms of life. A rose thorn embedded in the transparent larva of the starfish was found to elicit a cellular response to all intents and purposes the same as in animals possessing a vascular system. From these observations Metchnikoff came to the conclusion that phagocytosis is not merely an important feature, but the very essence of the defence against injury or infection; in other words, all the other phenomena of inflammation merely form the mechanism evolved by the higher forms of life to bring the leucocytes more rapidly to the field of action. This simple view is not, however, to be accepted. Whilst the leucocytic response is of undoubted importance, there are many other factors involved in the defence against infection.

The mechanism of leucocytic emigration and phagocytosis is one of great biological significance, and it is now generally agreed that these processes can best be explained by applying the known laws of chemistry and physics. They really depend upon the related properties of chemotaxis and amoeboid movement.

The term *chemotaxis* was suggested by Pfeffer in 1881 to describe a phenomenon exhibited by the spermatozooids of certain ferns which were powerfully attracted by dilute solutions of malic acid, a substance contained in the female sperm cell of the fern. A similar property was demonstrated by Stahl in his classical experiments with a jelly-like plasmodium growing on the bark of trees. Stahl showed that *in vitro* the plasmodium is attracted towards a drop of infusion of oak bark, provided it is in sufficiently dilute solution. Moreover, he noted that the plasmodium moves towards the drop by a process of protoplasmic streaming closely similar to amoeboid movement.

The chemotactic effect of a substance towards leucocytes may be tested by placing the substance in the open end of a capillary tube and inserting the tube within the peritoneal cavity of an animal, when positive chemotaxis is indicated by the aggregation of leucocytes round its open end. Many substances have a positive chemotactic action, whilst others are neutral, and others again are said to have a negative action, *i.e.*, repel the leucocytes.

Chemotaxis is now recognized to be a surface tension effect (see below). If the solution has the effect of reducing the surface tension of the leucocyte on the side nearest to it, the leucocyte travels in that direction. The property of phagocytosis also is now regarded as a comparatively simple physical process resulting from changes in surface tension. Phagocytosis is not, of course, peculiar to the leucocyte, but is enjoyed by all unicellular organisms and is one of the most striking characteristics of the amoeba. An amoeba may be looked upon as a drop of a colloidal solution enclosed in a delicate semi-permeable membrane, and its movements are related to changes in surface tension which, in turn, depend upon changes in the character of the cellular protoplasm or of the fluid in which it is immersed.

Both chemotaxis and amoeboid movement may be imitated by "artificial amoebæ" composed entirely of non-living substances. Thus a drop of clove oil suspended in a mixture of glycerol and alcohol

performs movements almost identical with those of the amœba—it responds to chemotaxis and exhibits “phagocytosis.”

Chemotaxis may be demonstrated if a small quantity of stronger alcohol is injected into the fluid near to the drop of clove oil. The alcohol reduces the surface tension on the one side of the drop, the drop thereupon bulges on that side and moves in the direction of the stronger solution. Phagocytosis is best imitated by an “artificial amœba” consisting of a drop of chloroform suspended in water. When such an amœba comes within range of a minute particle of shellac or paraffin or balsam, it sends out pseudopodia, engulfs the particle and then digests (*i.e.*, dissolves) it. If the particle is in the form of a thread, it may be engulfed even though it is several times longer than the diameter of the drop, being gradually drawn in and coiled up inside until completely ingested. Other types of particle, on the other hand, the chloroform amœba will reject, for example, fragments of glass or wood. The most remarkable of all is provided when a fragment of glass coated with shellac is offered to the chloroform amœba, for this compound particle is readily ingested, and when the shellac has been dissolved within the drop the glass is extruded.

Suppuration. Suppuration results when there is a nice balance between the infecting agent on the one hand and the inflammatory reaction on the other. The combined effects of the leucocytes and the antibodies contained in the inflammatory exudate have circumscribed the infection, yet failed to destroy the causative organisms. Many of the phagocytes are themselves destroyed by the bacterial toxins, and they and their enzymes and liquefaction products are the main constituents of the pus. In severe spreading infections the appearance of pus indicates that the infection has been circumscribed. Under these circumstances “laudable pus” is indeed welcome.

Pus formation is due essentially to the progressive emigration of leucocytes in large numbers, and it depends upon the continued production of chemotactic substances by the infecting agent. The pyogenic cocci are the commonest causes of suppuration, whilst coliform bacilli and many other organisms may be responsible, though less frequently. Aseptic irritants, *e.g.*, foreign bodies, are less common causes of suppuration.

The leucocytes present in pus secrete proteolytic enzymes, and as many of the leucocytes are killed by the bacterial toxins and undergo disintegration their intracellular enzymes are also liberated. The digestive action of pus is manifest by its effect in loosening adherent sloughs in such conditions as cellulitis. In any suppuration, indeed in any severe inflammation, there is inevitably some destruction of the specialized tissue cells, sometimes amounting to massive necrosis of the part. It is the function of the enzymes of pus to digest and liquefy such necrotic tissues, so that they may be re-absorbed or, failing this, discharged when the abscess comes to the surface.

This consideration should be kept in mind in the surgical treatment of suppuration. If pus is present the natural reaction of a surgeon is to let it out, to terminate the toxæmia caused by septic absorption from the abscess. It must be remembered, however, that the enzyme effects

of pus are often beneficial, and if the toxæmia from absorption is not too severe a more conservative attitude is often advisable, particularly in conditions characterized by extensive necrosis of tissues. This is the basis for the modern treatment of boils, carbuncles, acute mastitis and similar infections, delaying incision until the sloughs have been liquefied by enzyme action.

Types of Inflammatory Cells. In the foregoing account of acute inflammation and suppuration the cell of most conspicuous importance has been the polymorphonuclear leucocyte. This is the cell evoked by all the common causes of acute inflammation, and may be regarded as the first line of defence against acute infections. In the later stages of acute inflammation, and in chronic inflammation, other cells appear and occupy more important positions in the tissue reaction.

The *large mononuclear cell or macrophage* takes an important part in clearing up or scavenging after the acute phase of inflammation is past. This cell, variously known as a polyblast, a clasmatocyte, or an adventitial cell, is a large, pale, rounded cell with a vesicular nucleus and abundant cytoplasm. It is believed to be derived from the histiocytes or wandering cells of the tissues, from the cells of the reticulo-endothelial system, or possibly from the large mononuclear cells of the blood. Its main function is to scavenge by phagocytosis the *débris* left by the acute inflammatory reaction, and thus it may engulf red cells, dead polymorphs, blood pigment, foreign particles and fragments of dead tissue. In some cases, where there are larger fragments of foreign material to be removed, several macrophages fuse, forming giant cells allied to the foreign-body giant cells.

Lymphocytes are rarely seen in acute inflammations, except in the central nervous system, where they are regularly present in such conditions as poliomyelitis and meningitis. They are more characteristically present, however, in chronic infections and in specific conditions such as tuberculosis, syphilis and actinomycosis. Lymphocytes have little or no phagocytic activity, and migrate much more slowly than polymorphs in response to chemotaxis.

Plasma cells are also characteristic cells of chronic inflammatory conditions. They are mononuclear cells, somewhat larger than lymphocytes, with an excentric nucleus and a basophil cytoplasm which contains in its centre a clear area close to the nucleus. Plasma cells and lymphocytes together constitute the "small round cells" of chronic inflammatory exudates.

Eosinophil cells are normally present in the blood in small numbers (2 to 4 per cent.), and are occasionally found in inflammatory infiltrations. They are most characteristically present in allergic conditions and in parasitic infestations, and it seems likely they may appear in response to the irritation of foreign proteins.

Repair

Following rapidly upon inflammation, and indeed merging with its later phases, comes the process of repair. This process varies in character according to the particular type of tissue involved in the

inflammatory reaction and the degree of destruction. In general, the greatest capacity for regeneration is shown by areolar and fibrous tissues and by covering layers of epithelium, whereas the secreting cells of glands, the cells of the central nervous system and muscle cells undergo regeneration to only a small extent. In these latter tissues the process of repair consists mainly in filling the defect by fibrous tissue. Thus a wound of muscle is followed by very little proliferation of muscle cells, and the defect is repaired by a growth of scar tissue.

The process of healing may be seen in its simplest form in a clean incised wound of the skin. Microscopically, the first evidence of healing may be seen within 24 hours, both in the connective tissues and the epidermis.

In the connective tissues young capillary vessels bud out from exist-

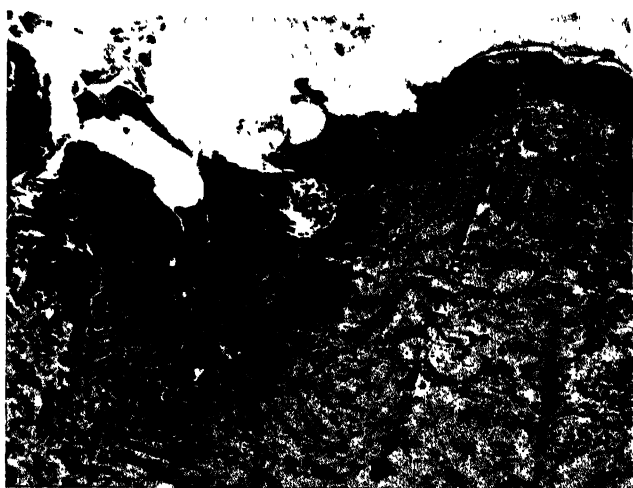


FIG. 1. Wound of integuments, twenty-four hours old. The cavity of the wound (on left) is filled with clot. Early inflammatory changes are seen at the margin.

ing vessels at the margin of the wound and invade the blood clot occupying the wound. Around the capillaries appear fibroblasts, and with them come large phagocytic cells, scavengers of any dead material. The fibroblasts proliferate actively and form a young connective tissue known as *granulation tissue*. Later the fibroblasts give rise to the formation of collagen fibrils, whilst the cells themselves become reduced in size and cease to proliferate, so that eventually the granulation tissue is converted into fibrous tissue of adult type.

Simultaneously with these changes in the connective tissues healing proceeds in the epidermis. At a very early stage epidermal cells extend from the wound margin into or over the surface of the blood clot. To some extent this process is due to multiplication of the marginal cells, but much of it is due to sliding of the adjacent epidermis in towards the wound. This is seen well in wounds of the rabbit's cornea. In this animal, pigment in the basal cells of the limbal epithelium forms a

complete brown ring round the limbus ; after a wound of the cornea sliding of the epithelium is demonstrated by centripetal displacement of that part of the ring close to the wound.

At first the new epidermis is thin and unkeratinized. Later it approximates to normal epidermis, but lacks sebaceous or sweat glands and hair follicles.

In large wounds healing is delayed by the simple difficulty of filling the defect. The same inflammatory reaction occurs, and the cavity of the wound is filled by a coagulum of blood and lymph containing many leucocytes. Capillary loops and fibroblasts grow into the coagulum from the surrounding tissues and sooner or later line the wound with



FIG. 2. Wound of the integuments, three days old. The cavity of the wound (left) is filled with clot. There is a vigorous downgrowth of epidermis over the edge of the wound.

granulation tissue, which later becomes fibrous. Contraction of the young fibrous tissue then occurs, and this has a valuable effect in reducing the size of the wound.

Whilst these changes are occurring in the depths of the wound the epithelium round the margin proliferates and grows over the defect as a thin blue layer, easily damaged by moving the part or by tearing off adherent dressings. In the case of large wounds, the epithelial growth may prove insufficient to cover the whole defect, especially if a chronic infection persists or if the part is of poor vascularity, for, owing to lack of adequate nutrition from the underlying connective tissues the epithelial ingrowth becomes progressively slower and the centre of the wound

is left open as an ulcer. In such cases the epithelium covering the wound margins is thin, blue and adherent, and is very easily devitalised.

Shrinkage of the tissues plays an important part in healing, particularly in large wounds. It is a matter of everyday experience that the eventual scar is always much smaller than the original wound, and in some cases the area of the raw surface is reduced by 75% as a result of this process.

Factors influencing the Rate of Wound Healing. The rate of wound healing is affected by many factors, both local and constitutional.

(1) *Vascularity.* Wounds of the face heal with great rapidity (despite constant movement) and so do wounds of the scalp, whereas wounds of the less vascular skin of the trunk and limbs are much slower. If the blood supply to a part is seriously diminished, as a result,

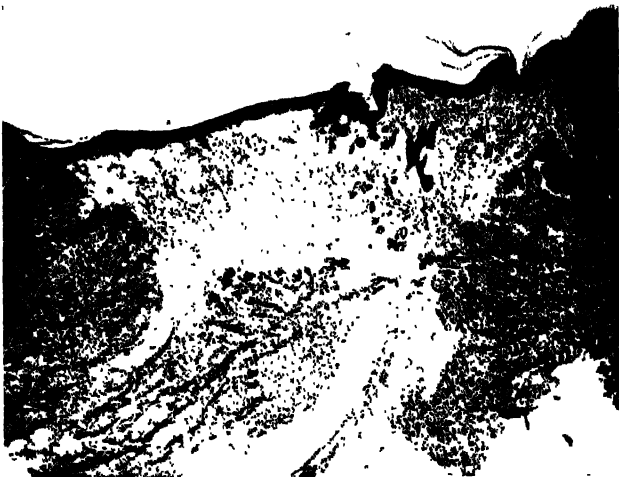


FIG. 3. Wound of integuments, ten days old. The wound is filled with young connective tissue and completely covered by epidermis. Some islands of epidermal cells are included in the scar.

for example, of local scarring or obliterative vascular disease, healing may be greatly delayed.

(2) *Lymph drainage.* Impairment of lymph drainage slows up the process of repair, as is seen clearly in the healing of a part œdematous from any cause. The beneficial effect of elevation of a wounded limb is due to the improvement which results in lymphatic drainage, while the effect of firm pressure, such as is produced by encasing the part in plaster, is attributable to the same cause.

(3) *Movement.* Movement of the wounded part is well known to delay healing, and indeed immobilization is a cardinal principle of treatment. Immobilization not only prevents damage to the young granulation tissue and covering epithelium, but also diminishes greatly the flow of lymph through the affected part, and this factor also appears to have a beneficial influence. Apart from delay in healing, movement also leads to the formation of large unsightly scars; witness the "keloid"

cicatrix of many wounds of the neck as compared with the thin linear and almost invisible scar in a limb immobilized in plaster.

(4) *Anchorage to subjacent tissue.* Reference has already been made to the part played by shrinkage of the wound. If the margin or base of the wound is anchored to a subjacent bone or ligament or fascia—the result, for example, of infection—shrinkage cannot occur and healing is delayed. This is well seen in the chronicity of varicose ulcer, of deep wounds involving bone, and of the incision in cases of osteomyelitis.

(5) *Foreign bodies and irritant applications.* Apart from inert materials such as stainless steel and vitallium, nearly all foreign bodies induce a reaction which impairs the process of healing. The reaction varies from a minimum connective tissue response to all grades of



FIG. 4. Wound of integuments, thirteen days old. High-power view showing character of the young fibrous tissue occupying the wound.* The epidermis is undergoing keratinization.

inflammation, according to the irritant character of the substance and the degree of infection associated. In the more severe types the whole process of healing is held up until the foreign body has been extruded.

Necrosis at the wound margin, whether due to impaired vascularity or to infection, has the same effect. Here healing is delayed until the dead tissue has been loosened by phagocytic action and cast off as a slough.

Antiseptics applied to a wound may have a similar effect inasmuch as they are harmful to the living cells. Indeed, some antiseptics are more effective in delaying the process of healing than the infection they are designed to prevent.

(6) *Infection.* Of all the local factors which influence wound healing infection is undoubtedly of the greatest practical importance. Toxins of bacterial origin destroy the marginal epithelium and connec-

tive tissue cells, and the presence of fluid and cellular inflammatory exudate also delays the healing process, while in some cases the formation of sloughs is a further factor. Much depends upon the nature of the infecting organism and it is generally agreed that a streptococcal infection is most harmful. The physical state of the infected wound is of even greater importance. Thus a completely open surface wound may heal at almost the normal rate despite heavy infection, while a deep wound, especially if closed by sutures, by creating conditions of tension under which necrosis occurs, may heal only after much delay.

(7) *Constitutional factors.* Wound healing is generally delayed in *diabetes* and *severe anaemias*. *Hypoproteinaemia* is believed to be a factor, perhaps to some extent on account of the oedema to which it gives rise. *Deficiency of vitamin C* has recently been shown to be important and may be the factor responsible for the delayed healing of operation wounds in patients suffering from gastro-intestinal diseases such as carcinoma of the stomach and peptic ulcer in whom the absorption of vitamin C has been defective. The frequency of "burst abdomen" in such cases has been attributed to this factor. It has been shown that the part played by vitamin C is to facilitate the restoration of collagen. In deficiency states the early phases of wound healing proceed normally, but collagen fails to develop, the wound does not consolidate and tends to stretch or give way at a later stage.

Wound-stimulating Substances. Since prehistoric times men have searched for substances capable of accelerating the healing of wounds. In recent years particular attention has been directed to embryonic extracts, some of which are known to accelerate the growth of cells in tissue culture, to various substances affecting surface tension, and to particular agents such as allantoin, red cell suspensions and chemicals with the sulphhydryl group (SH). At the present time none of these substances has been shown to be of practical value. Indeed, when one observes the headlong rate of healing as seen microscopically in a simple clean untreated wound, it becomes obvious that no method of hastening this process is likely to be more effective than that of putting the wound at rest and countering the influences adverse to healing.

CHAPTER II

WOUND INFECTIONS

THERE are no boundaries in scientific endeavour, and our knowledge of wound infections is the outcome of the labours of the pioneers of Listerian and aseptic principles and steady advances in bacteriology, immunology and therapeutic discoveries. Nowadays in hospital wards we seldom witness the once common ravages of erysipelas, moist gangrene and uncontrolled case-to-case infection. Though we may feel more secure, wound infections on a lesser scale are still very common and are a continued source of difficulty and anxiety in all fields of surgical work, so that study of the basic factors governing their origin, propagation and control is of the highest importance. Indeed, it is a first principle of surgical teaching.

Wound infection is the result of implantation of pathogenic bacteria upon or within a breach of the cutaneous, serous or mucous surfaces of the body. The portal of entry may be an obvious wound or the most insignificant abrasion, scratch or prick. In either case the ensuing infection may lead to severe damage to the part primarily infected, to grave constitutional disturbance and to lesions in distant organs, any one of which may exceed the original infection in importance and severity.

Predisposing Factors. Susceptibility to wound infection may be conditioned by constitutional or local factors. Frequently these are combined.

(1) In some persons, even though seemingly robust, there is an undeniable lack of resistance to certain types of infection, the underlying cause of which is not understood. Sometimes the susceptibility is familial, more often it is an individual peculiarity. Constitutional susceptibility may also be caused by debility resulting from acute or chronic illnesses, diet deficiency, diabetes, etc., which favour the occurrence and propagation of infection. The diminished immunity may be accounted for by impaired local tissue activity and by reduction in the bactericidal properties of the blood.

(2) The local factors which influence infection are largely governed by the quality of the leucocyte response. Consequently, parts which are highly vascular are relatively immune from severe infections and are more able to circumscribe them promptly and vigorously as compared with tissues of less vascularity. Thus wounds of the face seldom become infected, whereas in wounds of avascular structures, such as tendons or cartilage, the tissues show poor defence and often undergo necrosis.

The special characteristics of the wound may have an important bearing upon the severity and course of an infection. Contusions and

lacerations provide a favourable foothold for bacterial growth, especially if there is contamination with extraneous matter, and the resulting infection is often severe and attended by sloughing and considerable toxic absorption. Punctured wounds, such as may be sustained in conducting a post-mortem examination, may be equally dangerous, because infective material (sometimes with foreign matter) may be implanted at considerable depth and the narrow outlet prevents the escape of inflammatory products.

The skin and subcutaneous tissues are more resistant to infection than the serous membranes of the body. For example, a trivial infection of a joint, such as the knee, is often followed by severe and extensive inflammatory change.

Sometimes a part already infected, *e.g.*, a chronic ulcer, affords access for more virulent organisms, and the existing reactive processes may limit the severity of the infection. Superadded infection of more recent wounds is common, and sometimes of serious consequence.

Bacteriology of Wound Infections

The most important bacteria in the causation of wound infections are the pyogenic streptococci and staphylococci. In special circumstances there may be a concomitant or superimposed infection by other organisms such as *B. coli*, *B. pyocyaneus*, pneumococci, *Cl. tetani* and *Cl. welchii*.

The Pyogenic Streptococci. The streptococcus group is very heterogeneous and complicated classifications of various groups, types and strains have been formulated. For practical purposes, however, regard need be taken only of two chief types, the hæmolytic and the non-hæmolytic.

The hæmolytic streptococci are frequently found in the nasopharynx, and streptococcal infections may originate from this site or from external sources. They are apt to cause acute spreading infections such as erysipelas, cellulitis, lymphangitis, etc. They are of especial importance as the commonest cause of puerperal sepsis (p. 679).

As the manifestations of the diseases produced by the hæmolytic streptococci are so varied many attempts have been made to formulate a cultural or biological standard to account for the differences. Lancefield and others, approaching the problem from a serological standpoint, classify hæmolytic streptococci into groups according to their agglutination reactions. Most of the hæmolytic streptococci isolated from infections in human subjects belong to group A. Streptococci of other groups designated (B.C.D.E. and H. to K.), which have been obtained from a variety of human and animal sources, are, with few exceptions, non-pathogenic for man.

The non-hæmolytic streptococci (which lack diffusible toxins) have a much lower virulence. They are normally found in the mouth (*e.g.*, *str. viridans*) and the bowel (enterococcus). They are responsible for many low-grade infective processes, *e.g.*, dental sepsis, peptic ulceration, cholecystitis. They are common commensals in mixed infections. In rare instances anaerobic types of streptococci are encountered. They are usually non-hæmolytic and of low virulence.

Pathogenic streptococci elaborate a diffusible toxin which varies in amount and character in different strains. The toxin contains a leucocidin and a fibrinolytic agent, and it is probable that the virulence of different strains is governed by the extent of production of these substances.

Staphylococci. The staphylococcus group includes the commonest commensals and pathogens in man. These organisms occur in the throat, on the skin, in hair follicles and in sebaceous glands. There are two fairly distinct types, the highly pigmented *Staph. aureus* and the paler *Staph. albus*. Of these, the former is the more pathogenic in man and gives rise to pustules, boils, whitlows and carbuncles, and also to the great majority of cases of acute osteomyelitis.

The pathogenic power of staphylococci is due almost entirely to the exotoxins they produce. These contain (1) an α -lysin, which gives rise to skin-necrosis in addition to other toxic effects; (2) a β -lysin, of uncertain action; (3) a leucocidin; and (4) coagulase, which is responsible for the clotting of plasma. The toxins of staphylococci evoke a vigorous antitoxic response in the blood. Like other exotoxins they can be changed to toxoid by the use of formaldehyde, and in such attenuated form have been used for immunization.

Bacillus coli. The *Bacillus coli* occurs naturally as a commensal in the intestinal tract. It is a common cause, either alone or with other organisms, of inflammatory and suppurative lesions within the abdomen, e.g., peritonitis, cholecystitis, appendicitis. In such diseases the pus has a characteristic faecal odour. *B. coli* is also often responsible for inflammatory lesions in the urinary tract, e.g., pyelitis and cystitis. In general, the organisms cultivated from such lesions are more virulent than the ordinary intestinal strains.

Bacillus pyocyaneus. This organism, which occurs naturally in decomposing organic matter, sometimes gives rise to a superimposed infection in wounds. It rarely occurs alone. In wounds it gives rise to a characteristic green or bluish coloration of the pus owing to the production of a pigment pyocyanin.

Source of Wound Infections

A wound may be infected by organisms already present in the skin or mucous membranes, or by organisms introduced from without.

The skin is a common source of wound sepsis, for it frequently harbours pathogenic organisms, especially staphylococci and streptococci.

Skin organisms vary greatly in number and virulence. Some persons harbour staphylococci of high virulence in large numbers; others have relatively few pathogens. This disparity is related to certain occupations; thus doctors, nurses and others handling septic material may harbour dangerous organisms, and so to a smaller extent may butchers and fishmongers, whereas at the other extreme in motor mechanics and engineers working with oil and metal filings the skin of the exposed parts is commonly almost sterile.

Organisms introduced from without include the common pyogenic

cocci and also the streptococcus of erysipelas, the bacillus of tetanus, and the anaerobic organisms of gas gangrene.

Contamination of operation wounds is a subject of greatest concern to the operating surgeon, and one which places a great responsibility upon those who supervise the aseptic ritual at operations. Apart from its immediate effect in causing wound suppuration, such contamination may play a part in the ætiology of phlebitis and pulmonary embolism, and is doubtless of importance also in causing adhesions and leading to keloids and painful scars.

The incidence of wound infections bears a close relationship to the duration of exposure of a wound to the air. Thus in lengthy operations, *e.g.*, on the brain, a careful technique is of especial importance.

The commonest type of post-operative wound infection is the "stitch abscess," which usually develops ten days or two weeks after operation, giving rise to a small suppurative collection of low-grade virulence in the skin and subcutaneous tissue. The infecting organism is generally the staphylococcus albus, and is doubtless derived from the adjoining skin, in which it commonly occurs as a commensal.

More virulent infections of operation wounds are generally due to streptococci, and their invasion of the wound must usually be attributed to some breach of aseptic technique, although the possibility that the organisms may be endogenous, *i.e.*, blood-borne from some hidden focus of infection, cannot always be excluded with certainty.

Staphylococci derived from the skin of the surgeon or his assistants may occasionally be responsible for infection of operation wounds. It must be realised that the most thorough "scrubbing up" cannot render the hands completely sterile, that organisms lying within the skin glands may be carried to the surface by perspiration during the course of the operation, and that such organisms may escape through minute glove punctures or through the sleeves of the surgeon's gown, and thus contaminate the wound. In this connection it may be noted that unless particular care is taken, glove punctures occur in from 10% to 20% of operations. Fortunately, in most cases the organisms derived from a surgeon's hands are staphylococci of mild virulence, which readily succumb to the natural defence processes in the healing wound.

One of the most important sources of infection of operation wounds is the throat of the surgeon or his assistants. Pathogenic streptococci, hæmolytic and non-hæmolytic, are commonly present in the pharynx in a large proportion of persons, and their number and virulence are greatly increased in conditions of catarrh. The possibility of infection from this source (sometimes by "carriers"), should be a reminder of the necessity for adequate safeguards against droplet infection in operation theatres.

The importance of air-borne infections during operation was well recognized by Lister, and it was to guard against this danger that he introduced the antiseptic spray. Later, as the incidence of the more virulent hospital infections diminished, and the air of hospital wards and theatres became less subject to contamination, the need for air sterilization became less obvious and the carbolic spray was abandoned.

Recently, attention has again been turned to the risk of air-borne sepsis, and such methods as ultra-violet irradiation (Hart) or the use of fine antiseptic mists or aerosols (Pulvertaft) have been advocated.

SPECIAL TYPES OF WOUND INFECTION

Erysipelas

This is a rapidly spreading non-suppurative inflammation of the skin due to invasion by hæmolytic streptococci. The streptococcus is not specific and does not differ in its morphological and cultural characteristics from other streptococci, *e.g.*, those responsible for puerperal sepsis. It does, however, usually run true to type, and may spread from case to case if strict precautions are not observed.

The organisms gain access through a wound or abrasion, often so small as to escape notice, and invade the lymphatics of the dermis. In the great majority of cases erysipelas affects the face or head. It generally originates near the mouth or nose, and may spread over the whole face and scalp, but does not usually invade the neck. Occasionally erysipelas affects the trunk, the scrotum, or the limbs, gaining access at a wound or at such an infected surface as a chronic leg ulcer.

The affected skin is smooth, tense and fiery red. It is hot to the touch and tender on pressure. The spreading margin, which is irregular in outline, is clearly delimited and presents a raised edge, palpable on stroking towards the inflamed area. Minute vesicles are often visible, especially just behind the spreading edge. The fluid they contain teems with streptococci.

The inflammation tends to be arrested in parts where the skin is tightly bound to underlying tissues. In parts where the skin is loose, such as the eyelids, much swelling develops as a result of œdema.

Microscopically the corium is œdematous and infiltrated with innumerable polymorphs and wandering cells, particularly those of mononuclear type. Streptococci abound in the tissues and the lymph channels.

In most cases erysipelas (if untreated) continues to spread for from three to ten days and then terminates abruptly. If uncomplicated, it is generally not dangerous to life, except in infants and in old or debilitated persons. Immunity following an attack is of short duration; recurrences of infection may lead to considerable obliteration of the lymph spaces by fibrosis, and a form of elephantiasis may result.

Cellulitis

This is an acute diffuse inflammatory process affecting the subcutaneous tissues and other lax connective tissue planes. It is characterized by extensive necrosis and sloughing of the tissues, with scanty pus formation as a later and secondary feature. The infecting organism is generally the *Streptococcus hæmolyticus*, less often the *Staphylococcus*.

The infection may reach the subcutaneous tissues through a punctured wound or a comparatively small abrasion or prick, or from a neglected sore. The inflammation is often of sudden onset and spreads

rapidly, and may be attended by severe toxæmia. The affected part becomes red, brawny and tense, whilst acute lymphangitis may be indicated by scarlet coloration and intense tenderness of the surrounding skin, and by red lines outlining the course of the main lymph vessels leading to the regional glands. As the cellulitis progresses, the skin becomes transparent and shiny, and eventually becomes discoloured and separates, revealing grey necrotic sloughs beneath. In severe cases there may be massive necrosis amounting sometimes to gangrene of a part.

If the infection is of virulent type the regional lymph glands are involved early and may suppurate, or localized abscesses may develop at some point in the line of the lymph vessels. In severe cases septicæmia may supervene.

Septicæmia and Pyæmia

These two conditions are closely related and may be classified together under the term Septico-pyæmia. In septicæmia, organisms of the pyogenic group invade the blood stream and produce toxins which give rise to a characteristic illness. It is probably not true to say that the organisms grow and multiply in the blood stream. It seems more likely that the organisms establish themselves in the capillaries and sinusoids of the bone marrow, spleen and other tissues where they multiply and are liberated afresh into the blood.

In pyæmia, clumps of organisms or fragments of infected blood clot enter the blood stream from a suppurative focus and give rise to metastatic abscesses.

Septicæmia must be distinguished from bacteræmia or bacillæmia. These latter terms are simply used to denote the presence of organisms in the blood. A bacteræmia may be transient and symptom-free; a septicæmia is persistent and is associated with definite and often severe and continued intoxication.

Septicæmia. Septicæmia may originate from spread of the infection from an established suppurating focus or from a wound. Sometimes the origin is obscure and a pharyngeal or intestinal infection may be suspected, or puerperal or post-abortion sepsis.

Hæmolytic streptococci are responsible for over 50% of cases. The remainder are caused by staphylococci, pneumococci, and rarely *B. coli* or *B. pyocyaneus*.

Streptococcal Septicæmia is a common complication of puerperal sepsis, whilst another common cause is a punctured wound, often of trivial character, such as a pin prick. One of the most fulminating types of septicæmia is apt to follow a prick with an infected needle or instrument, sustained during a post-mortem examination. There are all too many cases on record in which such an apparently trifling accident has proved fatal within a few days.

The infection is characterized by severe toxæmia, with a high temperature, rapid pulse and raised respiratory rate. The parenchymatous cells of the viscera and the myocardium sustain cloudy swelling and fatty change, whilst in severe cases there are skin rashes and purpuric

hæmorrhages. Broncho-pneumonia and nephritis are common, especially in the terminal stages, whilst such complications as pleurisy, pericarditis, endocarditis, joint infections and multiple abscesses may occur.

Staphylococcal Septicæmia differs somewhat in its manifestations. It may occur as a complication of an infected wound, but is more apt to follow such staphylococcal lesions as a furuncle or a focus of osteomyelitis. It may arise from an infection of the tonsils or pharynx. The septicæmia is often of gradual onset, and at first its severity is not always apparent. Later it approximates in character to a streptococcal septicæmia. It is very apt to be complicated by the development of metastatic foci in the subcutaneous tissues, the viscera, and by pericarditis.

Pyæmia. Pyæmia results from the dissemination in the blood-stream of clumps of organisms or small fragments of infected blood clot derived from thrombosed veins in the neighbourhood of a suppurative focus. The causative organisms are the same as in septicæmia, but hæmolytic streptococci do not predominate to the same extent.

The source of infection is nearly always a collection of pus under tension in a cavity provided with free venous drainage. The commonest sources are osteomyelitis, infected compound fractures and infections of the lateral venous sinus secondary to middle ear disease. A special form, portal pyæmia or pylephlebitis, is a rare but dangerous complication of abdominal suppurations.

The infective emboli carried in the blood stream generally come to rest in the lungs, and there give rise to septic infarcts which later tend to form small abscesses. These in turn may form emboli, which lodge in the viscera, especially in the spleen and kidneys or in the skin or soft tissues. Abscesses in these situations may develop rapidly without causing much intensification of the toxæmia. In some cases, subcutaneous abscesses may appear suddenly, progress for a few days, and then as quickly diminish in size, the pus being absorbed partly or even completely.

TETANUS

Tetanus is the most dreaded variety of wound infection, and the mortality from the disease in the non-immunized is little under 50%. It is a local infection which causes a general toxæmia with a particular selective effect upon the motor centres of the medulla and spinal cord. It is the result of a specific anaerobe, the *Cl. tetani*, which though delicate itself, produces spores which are resistant to ordinary degrees of heat and high concentrations of chemicals. The normal abode of the organism is the intestine of horses and other herbivora, and it is sometimes present in human fæces. Heavily manured soil, street dirt, etc., are particularly liable to harbour the spores and are an obvious source of wound contamination especially in agricultural workers.

The tetanus bacillus thrives only in anaerobic conditions especially amidst devitalized tissue and in wounds already the seat of pyogenic or anaerobic infection. Suppurating wounds, such as may complicate

compound fractures, especially if there has been gross laceration and implantation of foreign material, are favourable for propagation of the organism; but the danger of infected abrasions, whitlows, and punctured wounds should be more fully realised lest timely prophylactic measures are neglected. The spores are sometimes introduced with a foreign body such as a splinter of wood and may lie dormant until disturbed by a subsequent operation. Imperfectly prepared catgut has been responsible for tetanus after surgical operations. In exceptional cases no portal of infection is discoverable.

At the site of infection, after an incubation period which may be as short as two, or as long as twenty-one days, a virulent toxin is liberated. The period may be prolonged to eight or more weeks if antitetanic serum has been given for prophylaxis. The toxin reaches the nervous system by the blood stream and along nerve trunks, and produces exaggerated reflex excitability within the motor cells, which is evidenced first by sustained spasticity in the related muscle groups and afterwards (if at all) by their spasmodic paroxysmal contraction. When the toxin reaches the nervous system it is at once fixed, and it cannot be detected in the cerebro-spinal fluid. Its effect seems to be purely physiologic because at death there are no changes in the brain and cord; death is due to secondary effects such as cardiac and respiratory failure, hyperpyrexia, exhaustion, and pneumonia.

The route by which the toxin reaches the nervous system has been the subject of a prolonged controversy and has invited much experimental research. In man it seems to be absorbed mainly by the blood because its earliest effects such as trismus, difficulty in swallowing and rigidity of the neck muscles emanate from centres which could be involved only through the circulation. Transmission of toxin along axis cylinders of motor nerves, though it may occur in man, is more usual in animals; it leads to tonic contraction of muscles in proximity to the source of infection (*local tetanus*), which, as the toxin diffuses, may become more widespread. In man the so-called *cephalic tetanus* which may complicate severe head wounds, probably owes its rapid onset, accompanied by convulsions and paralysis of cranial nerves, to migration of toxin along nerve pathways.

The features and the severity of tetanus (if not modified by prophylactic serum) are, *inter alia*, conditioned by the amount of toxin which reaches and may continue to reach the central nervous system. When only a small amount reaches the spinal cord there may be only local contraction of muscles in the region of the wound. When larger quantities pervade the nervous centres there is sustained generalized contraction of muscles, involving particularly the masseters, the muscles of the spine, chest, and abdomen and to a less extent the limbs; recurring reflex clonic contraction of the muscles may occur but it is usually slight and of short duration. Massive absorption of toxin causes a greater excitability attended by the classical reflex spasms brought on by the slightest stimulation. In the severest cases they may be almost continuous and lead to fatality from cardiac or respiratory failure, often preceded by hyperpyrexia (108° – 110°).

In tetanus it has been observed repeatedly that the intensity of the

disease (and its outcome) is closely related to its period of incubation; indeed, the incubation time is inversely proportional to the severity of the disease. Usually, too, in cases with a short incubation period there is an early onset of generalized muscle spasms which betokens an overwhelming toxæmia. From experience it has been found that when the incubation is under one week recovery is unlikely regardless of treatment.

GAS GANGRENE

Gas gangrene is the most serious complication of wounds. It has a fatal outcome in 50% of cases. The onset is acute and the infection progresses rapidly. Usually the disease is manifest within 24 to 48 hours of wounding, though in exceptional cases it develops within a few hours, and sometimes it is delayed for six or more days. Wounds of the buttock and lower limb are more often affected than those elsewhere, and the outcome of the disease at these sites is more grave.

The organisms are anaerobic spore-bearing bacilli of the *Clostridium* group and are derived from the intestinal tract of man and animals. The pathological features of the disease are due to the powerful toxins produced by the organism and to their continued multiplication and spread in the tissues, especially muscles.

In battle casualties gas gangrene is more prevalent in the winter months and in highly cultivated terrain than in the desert. Soiled garments are probably a frequent source of infection. In civil practice gas gangrene may complicate wounds contaminated with street dirt, manure and fouled clothing.

Generally several varieties of clostridia are responsible for the disease, though occasionally only a single species, e.g., *Cl. welchii*, may be present. The chief species causing toxæmia are *Cl. welchii*, *Cl. septicum* and *Cl. œdematiens*: the first two are locally destructive, *Cl. œdematiens* has a longer incubation period (2 to 5 days), is less invasive, but produces a very powerful toxin. In addition the wound may contain less pathogenic clostridia such as *Cl. sporogenes*, *Cl. tertium*, *Cl. bifermentans* and *Cl. fallax*. When *Cl. histolyticum* is present in mixed infection the disease is almost invariably fatal. Concomitant infection of the wound with aerobic organisms such as streptococci, staphylococci, pseudomonas pyocyanea and coliform bacteria is usual and may add to the gravity.

Predisposing Factors. It is very important to appreciate that clostridia are frequently present in wounds yet do not give rise to gas gangrene. The local factors in a wound which favour its occurrence are not fully understood. The chief known and suspected predisposing factors are :—

- (1) Inadequate drainage or excision of deep penetrating wounds.
- (2) Involvement of muscle.
- (3) The presence of foreign bodies, devitalized tissue, or collection of blood clot.
- (4) Impairment of the circulation of the part, by damage to blood vessels or by constriction in tight bandages or plaster of Paris.
- (5) The presence of soluble calcium, derived, for example, from highly fertilized soil.

Biological Properties of the Organisms. Henry showed that the special characters of gas gangrene depend upon the biological properties of the organisms concerned. All the organisms possess, in various degrees, the property of breaking down sugars and proteins, both of which are present in muscle. Some of the organisms, notably *Cl. welchii*, are strongly saccharolytic, and these appear to play the dominant part in the infective process. Others, particularly *Cl. sporogenes*, are strongly proteolytic, and their effect appears to be mainly synergic. Incidentally the proteolytic organisms are responsible for the gross putrefactive changes in the gangrenous part, and for the production of the peculiarly offensive gases.

In typical examples of gas gangrene due to *Cl. welchii* and *Cl. sporogenes*, it appears that *Cl. welchii* initiates the process and proliferates more rapidly. It generates powerful toxins which spread rapidly in the long axis of the muscle and kill the muscle cells, and since the toxins are strongly hæmolytic the muscle becomes stained by liberated blood pigment, and assumes a characteristic brick-red colour. In virtue of its saccharolytic properties the organism ferments the glycogen products, glucose and maltose, with the formation of acids and gases (carbon dioxide and hydrogen). This early rapid growth of *Cl. welchii* is succeeded by the more gradual development of the proteolytic organism *Cl. sporogenes*. The muscle in the neighbourhood of the wound, and later more distantly, undergoes putrefaction and becomes soft and diffuent, with the production of various organic alkalis and hydrogen sulphide and other noxious gases. As a result of combination of hydrogen sulphide with the iron set free from the blood by hæmolysis, the affected muscle acquires an olive-green colour, and finally becomes black.



FIG. 5. Gas gangrene. Transverse section of a muscle at an early stage in the disease. The muscle fibres are separated by fluid exudate. A few polymorph leucocytes are present.

It is interesting to note that the acid produced by saccharolytic organisms such as *Cl. welchii* tends to inhibit the growth of the organisms *in vitro*, but in wounds the acid is partly lost in the profuse discharge, and partly neutralized by inflammatory exudate, by calcium salts, and by the alkaline products of the proteolytic organisms.

Types of Gas Gangrene. The onset and progress of gas gangrene vary greatly in different subjects. The infection is sometimes

fulminating, and gas formation may be apparent within a few hours of the injury. In such cases the disease spreads rapidly, toxæmia is profound, and a fatal issue not long delayed. This *fulminating type*, common in war wounds of the thigh, is apt to occur, when the blood supply of a considerable part of a limb is impaired. In less fulminating, but nevertheless extensive infection, the gas formation may not be noticeable for 24 to 48 hours, and then toxæmia is rather less rapid in development. In this type several muscles or even the whole limb may be affected (*massive type*). In the less virulent forms of gas gangrene, seen more often in civil practice, the infection is limited at first to a single muscle or a single group of muscles, and these may become gangrenous from end to end, although neighbouring muscles

remain untouched (*group type*). Less commonly, there is no involvement of muscle, and the infection is limited to the subcutaneous tissues and fascial spaces.

The Pathological Changes. At first the affected wound has usually a dry surface, later there is a thin exudate (sometimes sanious) containing fat droplets: gas bubbles may be expressed from it. Organisms abound but leucocytes are scanty or absent. The wound at first emits a characteristic sweet odour. In the final stages the exudate is copious, dark in colour and offensive. The surrounding skin may be healthy or show mottling or greenish yellow patches in which large blebs may form. In an affected muscle the first recognizable change is a loss of contractility. Then the healthy colour is lost and gives place to a brick-red discoloration. Later the muscle becomes yellow and friable, and crepitates with gas bubbles, which are obvious at an early stage in X-ray films. Eventually it becomes soft and diffiuent, and its colour turns to olive green and finally black. It is noteworthy that the usual signs of inflammation and suppuration are absent.

Fig. 6. Gas gangrene. Transverse section of a muscle at a late stage in the disease. The muscle fibres are swollen and structureless, and many of them have undergone disintegration. Note the absence of polymorph leucocytes.

The gas develops with great rapidity, and bubbles rise continually into the wound. At first the gas is odourless, and, from its content of hydrogen, is combustible. Later hydrogen sulphide and the other products of proteolysis give it a characteristic odour. The wound exudes thin, blood-stained fluid.

From the region of the wound the infection spreads in the long

axis of the muscle to its two extremities, but for a considerable time extension in other directions is limited by the muscle sheath. Eventually this is perforated, usually alongside the blood vessels going to supply the muscle, and the infection may then spread to other parts of the limb.

Microscopically the first change apparent, near the spreading edge of the infected area, is that the muscle fibres are separated from their sheaths by an accumulation of fluid. This fluid is highly toxic, and by infiltrating in the long axis of the muscle and devitalizing the muscle fibres it facilitates the spread of the infecting organisms. The muscle fibres, surrounded by the fluid, lose their striations, and stain more deeply with eosin. Later the nuclei of the sarcolemma disappear and the whole fibre becomes necrotic. At a comparatively early stage the organisms are confined principally to the fibrous tissue reticulum of the muscle, and here they occur in large numbers. Later they invade the whole muscle.

Constitutional Effects. The constitutional effects of gas gangrene result principally from the liberation of exotoxins, and only in the late stages do the organisms invade the blood stream. The toxins are principally hæmolytic and cause extreme anæmia with slight icterus. Extreme degenerative changes occur in the liver, kidneys and other parenchymatous organs. The liver may be infected in the terminal stages, and becomes the seat of necrosis and gas formation. The adrenal glands undergo degenerative changes, and adrenalin disappears completely from the medulla.

Anaerobic Streptococcal Cellulitis and Myositis

The campaign in the Middle East brought to light an unusual but characteristic infection of the subcutaneous tissues and muscles caused by anaerobic streptococci with which are associated usually concomitant pyogenic organisms. It resembles gas gangrene, but differs from it in several important respects. It develops insidiously after an incubation period of 3 to 4 days with only mild systemic upset. In the wound there is usually a copious exudate and gas formation extending diffusely between muscle and fascial layers. The affected muscle is at first pale and boggy, next bright red, and finally dark purple. It retains its contractile power. The skin usually shows intense erythema. The odour of the wound is less sweet and not so pungent as in clostridial infection. It is important to differentiate this type of wound infection bacteriologically from true gas gangrene because it is more likely to be survived and more conservative measures suffice for its relief.

Progressive Post-Operative Gangrene of the Skin

An intractable form of infective gangrene of the skin and subcutaneous tissues may on rare occasions follow upon infected wounds. It has occurred most often soon after drainage of an appendix abscess or empyema. The gangrene involves the superficial tissues only and spreads slowly and progressively until very extensive areas are affected. At the spreading margin the tissues are raised, oedematous and under-

mined and extremely tender. There is usually moderate constitutional disturbance.

The bacteriological features of this form of gangrene have not been fully elucidated, but experimental observations suggest that it may be due to combined activity of a micro-aerophilic streptococcus (a type common in the intestine and in lung abscess) and a staphylococcus in the skin.

From the practical standpoint it is important to recognize that the gangrenous process cannot usually be checked by the ordinary surgical methods employed for infections, and that only free excision of the advancing serpygenous edges is effective.

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CHAPTER III

CONSTITUTIONAL EFFECTS OF INJURY

THIS title includes hæmorrhage and burning as well as the condition known as traumatic shock, and in addition the special complication known as the crush syndrome.

It is now established that hæmorrhage, burns and "shock" have many effects in common, and they may conveniently be studied together. Each is associated with a circulatory disturbance, so it will be of advantage first to review some of the more important factors concerned in maintaining the circulation.

The Mechanism of the Circulation. The circulatory system comprises the heart, the vascular bed (arteries, capillaries, veins) and the circulating fluid. In the traumatic disorders under discussion the heart's action is not impaired primarily, and indeed may be augmented to compensate for other defects. As a secondary development, however, the action of the heart may suffer, as a result either of anoxia or, when the venous return is insufficient, of impaired filling.

The arteries and veins also are not affected primarily, except perhaps in the acute reflex vasodilatation of syncope or "primary shock," and indeed in most traumatic circulatory disorders constriction of the arteries and veins goes a long way to compensate for the primary defect.

The capillaries, on the other hand, are affected very greatly. The capillaries, individually so minute, together form a network of vast potential extent. Normally only a small proportion of them are in active use and the remainder are contracted and empty.

Following trauma, the capillaries of the injured part are paralysed and dilate, while there may be a generalized capillary dilatation from anoxia or perhaps as a result of the absorption of depressor substances. Thus there results a disparity between the capacity of the vascular pathway and the volume of the fluid in circulation—a disparity increased by hæmorrhage or exudation of fluid into the tissues. It is this disparity which provides the key to the circulatory disturbance under consideration.

The Capillary Fluid Balance. The fluid content of the body comprises the intravascular fluid (blood plasma), the interstitial or tissue fluid and the intracellular fluid. The volume of intracellular fluid is almost constant, for alterations outside a narrow range are incompatible with life. The intravascular and interstitial fluids, on the other hand, vary greatly in volume. Interchange of fluid between the blood and tissue spaces takes place at the semi-permeable wall of the capillaries and is dependent on the following physical factors :—

(1) *The Capillary Hydrostatic Pressure.* This, the "blood pressure" within the capillaries, is greatest at the arterial end and diminishes

towards the venous end. It varies in different capillaries and at different times, and also depends upon the level of the capillary relative to the heart, but in general it is of the order of 30 mm. Hg. at the arterial end, falling to about 20 mm. at the venous end. Its effect is to force fluid out of the capillaries.

(2) *The Osmotic Pressure.* The osmotic pressure exerted by the plasma proteins is roughly 26 mm. Hg. Against this there is the osmotic pressure exerted by the colloids of the tissue fluids, amounting to about 4 mm. Hg. Thus on balance there is a pressure of about 22 mm. Hg., having the effect of drawing fluid into the capillaries.

(3) *The Tissue Pressure.* This depends upon such factors as the filtration rate, the rate of lymph flow and the elasticity of the tissues. It amounts to a pressure of about 1-3 mm. Hg., tending to force fluid from the tissues into the capillaries.

Thus it will be seen that at the arterial end of the capillary the hydrostatic pressure exceeds the sum of the osmotic and tissue pressures, hence fluid exudes from the vessel; whereas at the venous end the position is reversed and some of the fluid is reabsorbed (the remainder draining into lymphatic channels). Following injury this mechanism is upset and, according to the nature and extent of the injury, water (crystalloid solution), plasma or whole blood may escape into the tissues and stagnate there.

Fluid Loss

In different forms of injury the body may sustain an acute loss of water or plasma or blood. If the volume of circulatory fluid is sufficiently reduced a sequence of circulatory changes will occur independently of the character of the fluid loss. This sequence of changes will be considered later; first the differences depending on the character of the lost fluid will be studied.

Dehydration. Dehydration, by which is implied loss of either water or salt solution, is common in severe vomiting or diarrhoea or as a result of a combination of diminished fluid intake with loss by sweating or fistulous discharge. It does not occur in uncomplicated form as a result of injury but is an important factor in association with loss of plasma or blood.

In simple dehydration the blood undergoes concentration, as indicated by increase in the red cell count, hæmoglobin index and hæmatocrit ratio. Moreover, the plasma protein content also rises, and in consequence the capillary osmotic pressure is raised and water is drawn from the tissues into the blood stream. The sunken, lustreless eyes, the pinched drawn features and the dry inelastic skin bear testimony to this process.

Depletion of the extracellular fluid interferes with the transfer of metabolites between the blood and the body cells and causes anoxia. It thus seriously impairs the nutrition of such important tissues as the heart muscle, liver, kidneys and skeletal muscles. In addition as a result of the reduced flow of urine the non-volatile end products of katabolism are retained and diminution of the alkali reserve (acidosis) ensues.

Loss of Plasma. Certain forms of injury, particularly burns, are characterised by loss of plasma from the circulating fluid. The blood is thus deprived of proteins and fluid, while the cellular elements are retained. Examination of the blood therefore shows an increase in the red cell count, hæmoglobin index and hæmatocrit ratio, but a reduction in protein content. This latter feature is of great importance, for as the capillary osmotic pressure is reduced no fluid can be withdrawn from the tissues to make up the volume of blood in circulation. Indeed, unless the protein content is soon restored by mobilizing reserves the fluid shift will be in the opposite direction and œdema will result, with further reduction in the volume of the blood in circulation.

In plasma loss as in simple dehydration anoxia and acidosis will aggravate the disorder, while in addition the great hæmoconcentration by increasing the viscosity of the blood will further impede the circulation.

Hæmorrhage. When bleeding occurs rapidly and is copious the sudden acute loss of fluid from the circulation causes a sudden fall of blood pressure, which may be manifest in syncope or fainting. Very quickly, however, a compensatory mechanism is brought into action, which effects first (and almost immediately) a reduction in the capacity of the vascular bed, and secondly (and more slowly) a restoration of the blood volume.

The reduction in capacity of the vascular bed is effected by vasoconstriction, brought about by increased activity of the vasomotor centre, resulting from the fall in venous pressure and diminution in the depressor stimuli originating in the aortic and carotid sinuses. At the same time the heart rate is increased and its output thus somewhat augmented.

The restoration of blood volume is effected mainly by withdrawal of fluid from the tissues (a consequence of the fall of capillary hydrostatic pressure) and to a small extent by contraction of the spleen. This fluid replacement begins very soon after the hæmorrhage, but complete restoration of the blood volume takes many hours, or even days, according to the amount of fluid available in the tissues or made available by timely administration.

This fluid readjustment has important secondary effects on the composition of the blood. At first examination of the blood shows no departure from the normal, but soon there is evidence of dilution, as seen in diminution in the red cell count, hæmoglobin index and hæmatocrit ratio. Since full restoration of volume is slow, these estimations do not at first provide an accurate index of the amount of blood lost. There is also diminution in the protein content of the plasma, and if this is not rectified soon it will give rise to œdema.

In hæmorrhage, unlike simple dehydration and plasma loss, there is the additional factor of red cell loss, which by impairing oxygen transport increases the tissue anoxia. Since red cells are replaced slowly and hæmoglobin still more slowly the anoxia persists. This leads, in particular, to prolonged muscle weakness and especially to weakness of the myocardium.

Late Effects of Fluid Loss. Whatever the character of the fluid

lost, unless the loss is rapidly made good there develops a sequence of events which tends to maintain and may increase the circulatory embarrassment. This sequence has been called the death cycle (McDowall).

The sequence is somewhat as follows. The reduction in volume of the circulatory fluid unless completely compensated by vasoconstriction leads to a fall of blood pressure and reduced blood flow. Consequently the venous return is reduced, cardiac filling is impaired, the heart, despite an increase in its rate, fails to maintain its output, and the blood pressure is further reduced.

In addition to this simple sequence there are several collateral developments which influence the "death cycle." The factor of increased viscosity of the blood has already been mentioned. Other factors are consequences of anoxia, which may be due partly (in hæmorrhage) to lack of hæmoglobin, partly to slowing of the blood flow and partly to deprivation of tissue fluids. Thus anoxia damages the myocardium. It also weakens the skeletal muscles—the second heart—and they fail to pump blood back along the veins. Most important of all, it impairs the nutrition of the capillary endothelium, increases its permeability and promotes the escape of fluid from the vessels.

Traumatic Shock

The term "shock" has been applied to a wide variety of clinical states on no secure basis of pathology, and there are strong arguments in favour of discarding it. In this chapter the term is used merely as a convenient expression of the circulatory disorder resulting from injury.

In a typical case following a severe injury, the clinical progress is somewhat as follows. Immediately after the injury the patient collapses and may faint. This is the state of so-called primary shock. Although intense, this phase of collapse is not long sustained, and after a short time it may pass off completely. Later, generally within a few hours, signs of circulatory impairment reappear, the so-called secondary shock. This phase appears insidiously and if unchecked tends to progress and may prove fatal. At first the clinical signs are not definite. The patient is usually pale and limp and the pulse rate is somewhat rapid but the blood pressure may be normal or even raised. Only later, when the compensatory mechanism begins to fail, do the classical signs of "shock" appear.

It is now generally established that the early phase of syncope is the result of widespread vasodilatation, affecting both arteries and veins, with sudden fall of blood pressure. This vasodilatation is believed to be due to temporary paralysis of the vasomotor centre which is bombarded by painful and other afferent stimuli from the injured part, and perhaps also by stimuli from the higher centres.

The nature of the secondary circulatory disturbance has been the subject of numerous theories. It is accepted beyond all reasonable doubt that there is no primary heart failure (indeed the heart responds by increasing its rate and output) and no failure of the vasomotor centre (for compensatory arterial and venous constriction are obvious features) and that the primary and principal factor is disparity between

the volume of blood in circulation and the capacity of the capillary network. It is accepted also that in the later stages the progress of the circulatory failure is along the lines described above as the "death cycle." The main field for controversy is as to the cause of the disparity between the blood and the vascular bed. As to this, the views held most widely at the present time may be summarised as follows :—

(1) *Nerve Stimulation.* We have seen that in the initial phase of syncope following an injury it is generally agreed that there is a transient paralysis of the vasomotor centre as a result of bombardment by afferent stimuli originating in the injured part. In the past, many workers have suggested that the later circulatory collapse has a similar origin, the result perhaps of sympathetic inhibition or perhaps of excessive secretion of adrenalin. It has, however, been shown that even when the state of "shock" is severe both arteries and veins are in a state of active constriction, from which it would appear beyond dispute that the vasomotor centre remains intact.

(2) *Depressor Substances.* Cannon and Bayliss, in experimental work on cats, in which shock was produced by heavy trauma applied to the thigh, found that the shock could be prevented by clamping the iliac vessels during the experiments but appeared after the clamps were released. From this they assumed that the circulatory collapse was due to the absorption of a toxic or depressor substance from the injured part. A few years later it was shown by Dale and Laidlaw that widespread capillary paralysis could be produced by injection of histamine, and thus arose the conception of shock as due to absorption of histamine-like products from the damaged tissues. Later work, however, failed to confirm this hypothesis, for it was shown on the one hand that histamine shock is different in many respects from traumatic shock, and on the other hand that the histamine-like substances produced in an injured limb are insufficient in amount to account for the collapse which may result. Interest in depressor substances as a cause of shock has however been renewed recently by the discovery that a substance obtained from crushed muscle, possibly adenosine triphosphate, is capable of producing a shock-like state. Such a factor may possibly explain why severe crush injuries of heavy muscles are particularly prone to shock.

(3) *Local Fluid Loss.* After a severe injury the loss of blood by extravasation into the injured part may be considerable. In addition blood stagnates in the dilated capillaries of the part and, since the permeability of the capillary endothelium is increased, plasma escapes from the blood stream into the tissue spaces. Earlier workers, while recognizing the existence of this local fluid loss, considered that it was not sufficient to account for the circulatory disturbance. According to Blalock and his colleagues, however, the extent of the loss is greater than had been supposed. From experiments in cats in which, after traumatization of one thigh, the weight of the injured limb was compared with that of its fellow, he concluded that as much as half the total volume of blood in circulation may be lost in this way, an amount entirely sufficient to account for a severe degree of shock.

In man it is unfortunately not possible to assess the volume of fluid

lost into the injured part. In burns, where a large amount of fluid exudes at the surface in addition to that which accumulates in the tissues round and deep to the burn, it seems probable that this factor alone may be held responsible. In other types of injury the evidence is less convincing.

Whatever the nature of the primary factor in shock, clinical and experimental investigations in recent years have established many data of importance in relation to treatment, especially in relation to the three principal methods of treatment, rest, warmth and the administration of fluids. It is now realized that "rest" should imply strict immobility, for in the gravely injured patient even slight movements such as turning on one side gravely upset the blood pressure. The usual routine on admission to hospital of undressing and thorough cleansing may on occasions be fraught with danger.

The application of heat, formerly a cardinal principle of treatment, has also been shown recently to be dangerous if carried to excess. The blood vessels of the skin constitute a large part of the total vascular bed. In severe shock the skin capillaries are shut down—hence the characteristic pallor and coldness—and this should be regarded as a compensatory mechanism. The first effect of heat is to dilate these vessels and thus to increase the disparity between the blood volume and the capacity of the bed. Even in health, heat applied by a "shock cradle" for half an hour has been shown to bring about a notable reduction in the blood pressure.

Fluids may be beneficial or harmful according to their composition and rate of injection. The aim must always be to replace the type of fluid lost—blood, plasma, saline solution or water as the case may be—but two special factors must always be borne in mind. First, it must be remembered that capillary permeability is impaired in the injured part and also perhaps throughout the whole body, and in consequence crystalloid solutions given intravenously will quickly leave the circulation. Moreover, since a certain amount of protein is carried out too the osmotic pressure is reduced and more fluid is lost into the tissues. Secondly, it must be remembered that while in the early stages it is desirable to replace the lost fluids rapidly, in the later stages rapid injection may be dangerous, for if the venous pressure is raised too quickly the heart muscle, impaired as a result of anoxia, may be overtaxed.

Burns

Burns or scalds differ from other forms of physical trauma in that they affect primarily one of the most vascular and richly innervated tissues of the body, they are usually extensive, and they are always prone to infection. It is not surprising, therefore, that the circulatory disturbance caused by burns differs in many features from that due to other injuries.

Immediately after burning there may occur a transient phase of collapse similar to the "primary shock" which follows other types of injury, and probably due similarly to reflex vasomotor paralysis.

The most characteristic phase occurs somewhat later, however,

and becomes progressively worse during the succeeding two or three days. This phase, the so-called toxæmia of burns, has been attributed by different workers to a variety of causes, including suprarenal exhaustion, elevation of the blood potassium level, absorption of autolytic products from the burnt tissues, and sepsis. While the last two cannot be ruled out altogether—and indeed sepsis undoubtedly plays a part in some cases, though usually at a somewhat later stage—there is convincing evidence that the main factor concerned is loss of plasma.

This loss of plasma results from increased capillary permeability in the vicinity of the burn; some of the fluid accumulates in the tissue adjacent to the burn while there is a copious outpouring into blisters and as an exudation from the surface. It has been shown in animals that when the burn is extensive the fluid loss may amount to 60% or more of the plasma volume.

The blood changes follow naturally. There is marked hæmoconcentration, that is concentration of the blood cells as estimated by the red cell count, hæmoglobin index or hæmatocrit ratio. The protein content falls, and despite rapid mobilization from reserves may remain persistently below the normal. In some cases the reduction in blood protein is sufficient to induce generalized œdema. The potassium content of the blood may be raised; its significance is not understood.

While the importance of plasma loss is well established, it may not be the sole cause of the toxæmia of burns. Of other possible factors, the absorption of bacterial toxins is one of the most important. The risk of infection of a burnt surface is obviously very great; indeed it is almost invariable, despite the utmost care in treatment. Probably in most cases toxæmia resulting from infection assumes serious proportions at a somewhat later stage, *i.e.*, two or three days after the injury, though exceptionally there is evidence to suggest that it may be a factor within 24 hours.

Still later in the course of a burn—usually after two or three weeks—a further constitutional upset occurs characterized by hypoproteinæmia and deficiency of hæmoglobin. It is especially apt to happen in an extensive burn. While it in part may be due to prolonged infection, its causation is not fully established. It is important not only for its constitutional effects but also as a cause of delay in the healing of the burn.

✓ The Crush Syndrome

This syndrome is characterized by renal failure developing as a complication of a crush injury to a limb. It is especially apt to occur when a limb has been pinned under falling masonry and suffered a temporary interruption of its blood supply. The renal damage takes place when the circulation is re-established and is believed to be due to toxic breakdown products—particularly myohæmoglobin—derived from dead or dying muscle.

The marked changes in the crushed limb vary. As a rule the limb is swollen, hard, anæsthetic and paralysed. Arterial pulsation is generally absent, but may return, and as the circulation improves crops

of blisters appear. Necrosis of the muscles is a prominent feature, varying from patchy destruction to widespread gangrene.

In the kidneys the microscopic appearance is that of an acute tubular nephritis, with selective changes in the ascending limb of Henle and the second convoluted tubule. Brown casts of myohæmoglobin are seen within the lumen. It has been suggested that the level of the lesion is determined by the acidification of the urine which takes place at this segment of the nephron.

As a result of the renal damage, changes occur in the chemistry of the urine and blood. The urine is greatly diminished in quantity, is highly acid, and contains albumen and blood. Myohæmoglobin may be found within a few hours after release of the trapped limb. The blood urea and also the blood potassium rise steeply. The blood pressure is raised. Death from renal failure may occur with great suddenness.

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CHAPTER IV

TUBERCULOSIS

TUBERCULOSIS is one of the most widely distributed of all human diseases. All races are liable to infection and few escape. In Great Britain the death rate had shown an accelerated decline during the last few decades, but in spite of immense improvements in preventive measures and treatment it is still about 74 per hundred thousand of the population ; so that tuberculosis may be classed with venereal disease and cancer as one of the most important scourges affecting mankind.

Although tuberculosis in general comes within the domain of the physician, many of its local manifestations are at present regarded as within the scope of surgery. In the surgery of adults, tuberculosis of the lungs, the intestines, and the kidney and genital tract takes an important place ; and in the surgery of children, tuberculosis of lymph glands, bones, joints and the peritoneum accounts for as many as 30 to 40% of hospital cases. It is thus evident that a knowledge of the pathological background of the disease is of importance to every surgeon.

Frequency. The most accurate method of assessing the true incidence of tuberculosis is by routine post-mortem examination. This has been carried out by many workers in different parts of the world, and the recorded results are very instructive. Naegeli (Zürich) found that 71% of 500 bodies of all ages were tuberculous, and that amongst adults over 18 years of age 98% were definitely infected. Reinhart (Berne) recorded similar findings in a series of 360 cases. In Edinburgh, Todd, who conducted a thorough examination of 404 bodies, found that death was due to tuberculosis in 18, and that in 68.9% of the remaining 386, there were signs of tuberculous infection. In the Royal Hospital for Sick Children in Edinburgh (children under 12 years) Agnes Macgregor found in 1,127 autopsies (from 1922 to 1929), that tuberculosis, in some form, was present in 22% of cases, and that in no less than 18% it had been the cause of death.

Tuberculosis is a disease influenced notably by racial and economic factors, and these figures, which are from unselected communities in populous areas, indicate that the majority of adults and many children manifest some evidence of tuberculous infection, and that the lesion may be quiescent or progressive. The figures from children's hospitals show how frequently infection occurs in early life. This is of importance, because it is generally believed that the majority of people acquire a tuberculous focus (become tubercularized) before adult life, a belief substantiated moreover by the observation that the Mantoux skin reaction is positive in 50% of children under 12 years of age,* in over 70% at 20 years. As will be emphasized later, there is considerable pathological evidence that many of the visceral manifestations

of tuberculosis seen in adult life owe their origin to the recrudescence of infection acquired in early life, rather than to an infection acquired later.

Resistance to Tuberculosis. Resistance to tuberculosis varies in different races, at different ages, and from time to time in the same individual. Usually infection acquired in the first two years of life is rapidly fatal from progressive lesions, an observation which emphasizes the importance of protecting young children from sources of massive or continuous infection. After the age of three years tuberculous infection, though more likely to be progressive than in older children, may remain quiescent or may even become arrested. In most civilized races there is a high resistance to tuberculosis, the result of progressive immunization during many generations, but in isolated communities, not previously immunized, the resistance is lacking. When members of such communities are subjected to infection they show an extreme susceptibility to the disease, which may then take an epidemic form of great virulence. Very striking examples of this are provided by the recorded outbreaks of tuberculosis in Canadian Indians, Senegalese, and other uncolonized peoples. Tuberculosis was practically unknown in the Indians of the great Canadian plain until about 1870-1880. At that time the influx of traders, half-breeds, and tuberculous Indians of other tribes subjected them to infection, which quickly became rampant. By 1890 the disease had assumed epidemic form, and eventually 26% of the adults and 32% of the children died of tuberculosis. Even at the present time, in spite of improvements in hygiene and treatment, the death rate is twenty times that of the white population in adjoining districts.

In Scotland, the Outer Hebrides provide a very instructive example of how devastating was the introduction of infection into communities which, until comparatively recently, had been free of tuberculosis. In these islands the introduction of infection is almost within living memory, and the annual mortality from tuberculosis is almost double that of the rest of Scotland.

The rarity with which doctors, nurses, and others in sanatoria develop active tuberculosis, though constantly exposed to infection, is explained, *inter alia*, by an acquired resistance in early life. For a similar reason, a wife seldom acquires infection from a husband with "open" pulmonary tuberculosis, though children in the home frequently do.

The above observations suggest that infection with tubercle bacilli is less unfortunate than would be supposed, provided the infection does not occur in the first few years of life, and is not of too overwhelming virulence when it occurs. This conception was the basis of the practice of inoculating babies against tuberculosis by means of an attenuated culture of tubercle bacilli (B. bilié, Calmette-Guérin; B.C.G.) in order to evoke deliberately the defensive processes against subsequent infection.

Although infection with tuberculosis early in life may have a partial immunizing effect, it is insufficient to afford protection against massive super-infection at a later period.

Heredity and Tuberculosis. Congenital tuberculosis, the result of

transplacental infection, is of great rarity. Recent observations have shown that in such cases the maternal uterus has been the seat of tuberculosis.

Statistical evidence is very conflicting in regard to the extent to which there is a specific *hereditary predisposition* to tuberculosis. The hereditary factor is important to the extent (as in other diseases) that some families have more than others tissues favourable for the survival of tubercle bacilli. Variation in susceptibility is dependent more on variation in environment than on specific susceptibility.

Types of Infection. There are two common types of tubercle bacillus, the human type and the bovine type. The two are similar in appearance, and they can only be differentiated by culture or by animal inoculation. When cultured on glycerine-egg medium the human type grows readily, producing in the course of two or three weeks an abundant wrinkled growth, whereas the bovine type grows hardly at all. When inoculated into animals the bovine type is more virulent than the human type. An emulsion of 0.1 mgm. of dried bacilli of bovine type injected intravenously in rabbits causes generalized tuberculosis and death within two months, whereas after a similar dose of the human type the animal dies only after two months, or may survive.

Both human and bovine types occur in man, and the frequency of each type varies in different organs and tissues. Bovine infection is generally regarded as more virulent, and more likely to give rise to multiple lesions or to generalized infection. With few exceptions intrathoracic tuberculosis at all ages is due to infection by the human type of bacillus; whereas, tuberculosis of lymph glands, bones and joints, and the abdomen, especially in children, is due in a considerable proportion of cases to the bovine organism. In Glasgow, Blacklock found that in children up to thirteen years bovine infection accounted for 64% of cervical gland tuberculosis, 80% of abdominal, and 35% bone and joint tuberculosis.

Griffith (1932) gave the following results of his investigations of the incidence of bovine infection in the principal forms of "surgical" tuberculosis :—

Site of Disease.	All Ages.		0 to Four Years.		Five to Fourteen Years.	
	Number of Cases.	Per cent. Bovine.	Number of Cases.	Per cent. Bovine.	Number of Cases.	Per cent. Bovine.
Cervical lymph glands						
(England)	116	45.7	21	85.7	54	48.1
„ (Scotland)	114	73.6	53	84.9	71	74.6
Bones and joints (England)	520	18	88	27.3	351	18.5
„ „ (Scotland)	196	42.8	86	60.5	65	38.5
Genito-urinary (England)	23	17.4	—	—	3	33.3
„ (Scotland)	22	9.1	—	—	5	40.0

Sources of Infection in Man. The most common sources of infection are : (1) sputum from infected subjects ; (2) contaminated milk from cows suffering from tuberculosis of the udder.

A phthisical patient may convey infection directly to those about

him through his sputum, or the sputum may become inspissated, and may then be carried by dust. In either instance infection may occur by inhalation or by ingestion.

Milk is a common vehicle for the tubercle bacillus, and so greatly is this source of infection dreaded in some cities that all milk is pasteurized before consumption. Improved veterinary and municipal administration has of late years reduced gradually the frequency of this source of infection, yet at least 7% of raw market milk in this country contains tubercle bacillus.

Portals of Entry of Infection. Tubercle bacilli may gain access to the body by the mucous membranes or, rarely, by the skin. The



FIG. 7. Calcified tuberculous nodules in the lungs and tracheo-bronchial lymph glands.

mucous surfaces of the respiratory and alimentary tracts are undoubtedly the commonest sites of entry of infection, and there need be no breach of the surface for its occurrence.

Infected droplets of sputum or particles of dust may be inhaled so that bacilli reach the pharyngeal or respiratory mucosa, which they penetrate. That bacilli may gain entry to the body by the pharynx is proved by the discovery of tuberculous foci in the tonsils of children; and it has been estimated that at least 5% of excised tonsils show microscopic evidence of tuberculosis. The mucous membrane of the trachea or of the bronchi also affords a surface for infection, and it is believed that catarrh of these passages favours its occurrence. Post-mortem and radiographic examination in children has shown that primary involvement of the lung tissue (with secondary infection of the

tracheo-bronchial glands) is more common than was supposed formerly—the so-called *primary complex*.

The mucous membrane of the small intestine is the other great absorptive surface for tubercle bacilli, and the infection is almost



FIG. 8. Tuberculosis of the kidney. At the upper pole there are two cavities, lined by tuberculous granulation tissue, which communicate with the renal pelvis. At the mid-part of the kidney there are masses of caseous material. Multiple small tubercles are present in the mucous membrane of the renal pelvis. The ureter is infiltrated and greatly thickened.

(Department of Surgery, University of Edinburgh.)

always of bovine type carried by milk. Unlike most other organisms the tubercle bacillus, in virtue of its fatty capsule, can survive exposure to the gastric juice, even for a period of several hours, and thus reaches the intestines unharmed. The bacillus gains access to the tissues through the lymph follicles of the ileum, the most actively absorptive region of the gut. Sometimes local ulcerations of the mucosa are present, but usually the point of entry is not detectable.

Infection through a cutaneous surface is very rare, and is limited almost to those frequently in contact with infected material. It is consequently most apt to affect doctors, orderlies, or butchers. The organism gains access through an abrasion, and there sets up a localized focus (*verruca necrogenica*), which is usually situated on the hand, wrist or arm.

The Early Evidences of Tuberculous Infection. To begin with, tuberculosis is always a local disease, and it affects especially the lymph vascular system of the body. It is therefore in the regional lymph glands and vessels draining the pharynx, lungs and small intestine that one seeks evidence of early infection. The initial foci of tuberculosis are usually found at one or more of the following sites : (1) the tonsils, (2) the cervical lymph glands, (3) the tracheo-bronchial glands (by far the commonest), and (4) the mesenteric glands. From the group of glands first involved the infection may spread to others. The affected glands may show little or no macroscopic evidence of disease, but usually one or several glands become enlarged, and may cascade. Later in life, if resistance proves adequate, the only evidence of former tuberculous infection may be calcification of a gland, and such hard nodules are often noted in the mesentery of the small intestine, the lung roots, and less often in the neck.

Progress and Spread of the Disease. The progress of tuberculous infection depends on the virulence of the bacilli and on the patient's powers of resistance.

In some subjects the original infection is followed by progressive tuberculous disease. In the vast majority the resistance proves adequate, and the organisms are either destroyed or entrapped in scar tissue. In others again the infection may remain latent during many years, and may later become reactivated and spread, if for any reason the resistance is lowered.

Natural resistance is low in the first few years of life, but becomes greatly increased in later childhood. The resistance may be undermined by malnutrition, intercurrent illness, or unhealthy environment, or by a combination of these factors.

The disease may spread in any of the following ways :—

- (1) By the lymph vessels.
- (2) By the anatomical passages.
- (3) By the blood.

(1) *By the Lymph Vessels.* This is quite the most important mode of spread in the early stages of tuberculosis, which is primarily a disease of the lymphatic system. From the lymph glands earliest involved, in the neck, mediastinum or mesentery, the disease spreads first to adjacent glands of the same group, and later to glands of other groups. Further extension by lymph channels or by apposition leads to the infection of other tissues and of viscera. From the mesenteric glands extension to the subserous lymph channels may cause tuberculous peritonitis. Spread from the abdominal lymph vessels to the thorax is sometimes noted, and this may occur along the line of the internal mammary vessels. In the thorax the disease may spread from the glands at the hilum of the lung to the peribronchial lymph vessels and

to the lung and pleura. In the neck the glands on both sides may be infected, and from there the disease may spread to the mediastinum or the axilla.

(2) *By the Anatomical Passages.* The most striking example of this method of spread is seen in tuberculosis of the larynx and of the intestines in phthisical patients, for it is generally accepted that these lesions are the result of infection from coughed-up and swallowed sputum. A similar method of spread is witnessed in the lungs, where bacilli gaining access to the lumen of a bronchus from an ulcerating lesion may be responsible for extension elsewhere in the lungs.

It is said also that infection from a tuberculous kidney may be carried in the urine to the bladder, and it seems more probable that infection along the ureter spreads by contiguity of tissue rather than within the lumen.

(3) *By the Blood.* The blood stream is an important channel for the spread of tuberculosis to the viscera. The bacilli may reach the blood stream as a result of ulceration of a venule in an infected lymph gland or in an ulcerative process in the lung or other viscus.

The visceral manifestations of tuberculosis—*e.g.* in bones and joints, kidney, epididymis, etc.—are believed to be due to dissemination *viâ* the blood stream. It seems probable that an active primary lesion in a gland or in the lungs may disperse showers of organisms into the blood stream from time to time. Many organisms are doubtless destroyed, but they may take root and lead to single or multiple tuberculous foci in the tissues in which they lodge. In this way may originate a solitary focus in one kidney or a bone or joint. If, on the other hand, a large number of blood-borne organisms survive, they give rise to multiple foci in many tissues and viscera and thus lead to the condition known as *acute miliary tuberculosis*. In rare instances miliary tuberculosis assumes a chronic form and is sometimes survived.

Elimination of Tubercle Bacilli: Tuberculous Bacilluria. Tubercle



FIG. 9 Tuberculosis of the epididymis. Both globus major and globus minor are enlarged and contain numerous caseous foci. The ductus deferens is thickened and nodular. The body of the testis is affected.

(Museum of Royal College of Surgeons of Edinburgh.)

bacilli may be excreted in the urine in cases of active tuberculosis of the lungs, bones and joints, lymph glands, etc. The bacilluria is usually symptomless, but there are always pus cells in the urine. The bacilli are not eliminated from the kidney by a process of simple filtration from the blood, but originate in minute and usually microscopic foci situated close to the cortical glomeruli. The small foci in the kidney are usually non-progressive and, after a variable time, undergo fibrosis, but, in a few cases, renal tuberculosis may develop at a later date.

In the same way, tubercle bacilli may be present in small numbers in the cerebrospinal fluid without evidence of meningeal origin. They originate from small overt foci in the brain substance.

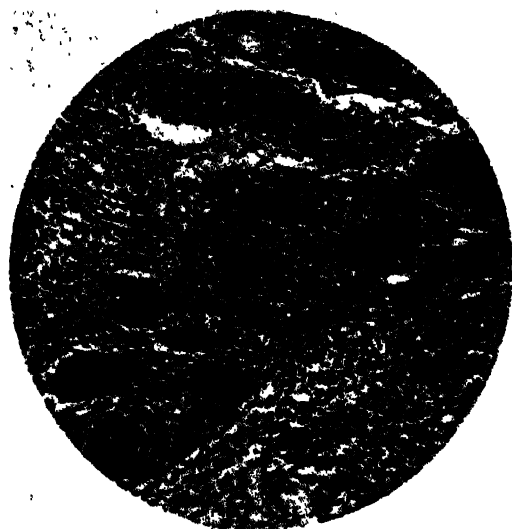


FIG. 10. Section of a tubercle (low power). In the centre there are endothelioid cells and giant cells, while above and below there are collections of lymphocytes. There is no caseation.

(Laboratory of Royal College of Physicians of Edinburgh.)

Relative Resistance of Organs and Tissues to Tuberculosis. It is a commonplace that certain organs and tissues are especially susceptible to tuberculosis, others relatively resistant. Lymph glands, the lungs, the intestinal tract and peritoneum, bones, joints and bursæ, are commonly affected, whereas the thyroid, heart and skeletal muscles are almost immune.

In some organs and tissues the resistance continues even after the disease has estab-

lished itself locally, whereas in others it diminishes once the disease has gained a foothold. The lung shows definite evidence of resistance as indicated by fibrosis even when extensively diseased, whereas the meninges once involved show no such reaction. The behaviour of the kidney is paradoxical, for it may eliminate innumerable bacilli during long periods and yet remain relatively unharmed, but when once it becomes the seat of tuberculosis it undergoes extensive destruction, and rarely heals. Similarly the suprarenal gland is affected seldom, but when involved exhibits poor resistance, and its fellow often becomes infected also.

The Local Lesions of Tuberculosis. The characteristic lesion of tuberculosis, *i.e.*, the local reaction of the tissues to the presence of tubercle bacilli, is the tubercle or tuberculous follicle. Such a follicle consists of endothelioid (epithelioid) cells and lymphocytes, collected in a more or less spheroidal mass around a clump of bacilli. The endothe-

lioid cells, which occupy the central parts of the young follicle, are oval or spindle shaped cells with faint-staining nuclei and abundant clear cytoplasm. They are believed to be derived from the endothelium of blood and lymph vessels and from the fixed connective tissue cells of the part.

The lymphocytes, which are believed to be derived from the proliferation of local perivascular lymph aggregations, are generally arranged in a more or less circular zone near the periphery of the follicle.

Another constituent of the typical tuberculous follicle is the giant cell. This is a large cell of irregular shape, and often ill-defined at its margin. It contains numerous small oval or rounded nuclei, which typically are situated near one edge of the cell or are disposed in horseshoe formation. Commonly one or more such giant cells occur in a single follicle, and they are usually situated near the margin of the region of endothelioid cells. They are believed to be derived from an endothelioid cell in which amitotic division of the nucleus has been unaccompanied by corresponding cleavage of the cytoplasm. They are regarded as foreign-body cells of special

type, and when present in cellular collections such as have been described they are very characteristic of tuberculosis. They are not, however, invariably present nor entirely pathognomonic of tuberculosis.

The above description is that of a tubercle in the earliest stages of its development, a tubercle which from its smallness may be described as a *miliary tubercle*. Very soon after its formation, however, the tubercle undergoes further changes, and the first and most important of these is *caseation*. This is a form of coagulation necrosis affecting the endothelioid cells near the centre of the tubercle, and it is now generally attributed to the action of toxins set free from the bacilli around which the tubercle has formed. The endothelioid cells affected in this manner become swollen and lose their outline, their nuclei become faint and disappear and eventually the cells fuse in a dry, homogeneous mass of *débris*, which from its naked-eye resemblance to cheese is known as caseous matter.

From its inception a tubercle is completely devoid of blood vessels. This avascularity is attributable to the action of the bacillary toxins, which effect a necrosis of the capillary walls and an obliterative



FIG. 11. Section of a tubercle (low power). A typical tubercle is seen, with central area of caseation surrounded by lymphocytes and endothelial cells. Two giant cells are evident.

(Department of Pathology University of Glasgow)

endarteritis in the larger vessels of the surrounding tissues, and it is of special significance in that it tends to prevent the access of organisms to the blood stream.

Further changes in the tubercle depend upon the virulence of the disease and upon the reaction of the tissues. If the disease does not progress the tubercle becomes surrounded by fibrous tissue and may ultimately become almost obliterated in a dense scar. Such "healed tubercles" are common in the lungs and in lymph glands. Frequently they undergo calcification, and are then recognizable in radiograms. If, on the other hand, the disease progresses, new tubercles develop in adjacent lymph tracts, and by confluence they may form foci of large size.

Occasionally, as for example in the meninges or, rarely, in a joint, the disease may progress with great rapidity from the onset, and the microscopic appearance may be that of an acute inflammation, with an exudate of fibrinous fluid and an infiltration of polymorph leucocytes (*acute tuberculosis*). Much more commonly, however, the course of the disease is slow and tractable, and is marked by a fairly even balance between the invading organisms on the one hand and the resisting tissues on the other (*chronic tuberculosis*). At the margin of a focus the process slowly extends, its path partly barred by fibrous tissue derived from the surrounding stroma, whilst at the same time the central zone of caseation gradually enlarges, sometimes to such an extent that entire organs, *e.g.*, the kidney and the suprarenal gland, become completely caseous.

In certain situations, notably in bones and lymph glands, the caseous material is apt to undergo softening, and, by admixture with polymorph leucocytes, to become caseous pus, forming a cold abscess.

Hypertrophic Tuberculosis. In the ileocaecal region, in joints, and rarely in the stomach, the tissue response to tuberculous infection does not result in typical follicles but takes the form of a diffuse overgrowth of granulation tissue and young fibrous tissue, the so-called hypertrophic form of tuberculosis. Microscopically, caseation is lacking, and giant-cell systems are scanty or even absent. In the ileocaecal region this form of tuberculosis leads to great thickening of the wall of the gut, and subsequently the contraction of fibrous tissue causes much narrowing of the lumen and binds the caecum, appendix and ascending colon in a firm shrunken mass. In joints the synovial membrane is replaced by a proliferating mass of granulation tissue which spreads in the form of a pannus over the articular cartilage and fills the recesses of the joint.

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CHAPTER V

ACTINOMYCOSIS

ACTINOMYCOSIS is a disease resulting from infection by the *streptothrix actinomyces*, and the lesions to which it gives rise belong to the group of infective granulomata. It affects especially the mouth, abdominal organs and lungs, and is characterized by the formation of much granulation tissue and by fibrous infiltration and multiple abscesses. The disease is common in cattle, and is by no means rare in man.

"Pin head" granules, greenish-grey in colour though sometimes bright yellow like grains of sulphur, can usually be found in the invaded tissues or in the pus. These granules are compact colonies of the streptothrix, which grows as a mycelium or felted mass of branching filaments (hence the term "ray fungus"). Occasionally the filaments are fragmented into bacillary or coccial forms, and occasionally there are rows of oval or spherical spore-like structures or gonidia. The filaments are Gram-positive, and grow only at about body temperature.

There are several types of *streptothrix actinomyces*, but the only type responsible for actinomycosis in man is the organism isolated by Israel and Wolff. The organism is a non-acid-fast anaerobic streptothrix. It has been isolated from the tonsils, carious teeth and alimentary canal of healthy persons; and the view is now held that one or other of these sites is the source of infection. In actinomycotic lesions the streptothrix is often associated with other bacteria, sometimes as a gross infection, e.g., with *B. coli*, but always in conjunction with a minute Gram-negative organism—*bacillus actinomycetum comitans*. The associated bacteria are believed to furnish favourable local conditions for the invasion of the streptothrix and its proliferation, probably, as has been demonstrated in the case of the tetanus, by reducing the oxygen tension in the tissues to a limit which will allow the anaerobic spores to germinate.

Cultivation of the actinomyces from pus is difficult because it is frequently contaminated by organisms which, on account of their greater viability, outgrow the streptothrix in culture media. The difficulty may be overcome by repeated mixing and shaking of the pus in saline: the actinomycotic granules sink on standing and may be seeded independently into culture media. The most suitable media are blood agar, glucose agar, or serum agar, and cultivation is carried out aerobically and anaerobically. The colonies, on agar plates, are dull white and round with filaments radiating into the surrounding medium.

Methods of Infection and Transmission. The recognition, bacteriologically of different varieties of the streptothrix actinomyces and the identification of the type specific for human and animal lesions has helped to dispel the uncertainties as to how infection may be acquired.

The older view of the mode of infection was that actinomycosis was

essentially a disease of persons who lived in rural areas, and that they acquired it from grain seeds in the same way as cattle. Support for this belief seemed to be afforded by the observation that people engaged in certain occupations, such as harvesters, dairy workers, and stable attendants, were prone to suffer from the disease; and that in a number of instances there had been a history that infection had followed abrasions of the mouth or tongue by grain husks or stalks, etc. But in contradiction of this exogenous source of infection there is no authentic record of transmission of the disease from man to man or from animal to man; and, furthermore, later evidence indicates that the incidence in country is no greater than that in town dwellers. The association of foreign bodies with the disease has probably been overstressed; and now there is conclusive evidence that the streptothrix may be a normal inhabitant of the oral cavity and gastro-intestinal canal of man and animals, leading there a saprophytic existence until local tissue injury affords an opportunity for the organism to gain a footing. In support of the now accepted view of endogenous infection, it is known that the *actinomyces bovis* is a very delicate organism which is not found outside the body and grows most readily if furnished with a limited supply of oxygen.

Site of Infection. The commonest site of infection in man is the mucous membrane of the mouth. The actual mode of infection is often doubtful, and it may be impossible to trace its source. Sometimes infection may be initiated by injury caused by foreign bodies, but there is little doubt the frequency of the association of foreign bodies with the disease has been exaggerated.

In some instances the site of infection is the mucous membrane of the intestine, or, less often, of the bronchi. In rare cases infection of the skin and subcutaneous tissues has followed an abrasion.

Characters of the Lesion. The affected area is infiltrated by a firm fibro-cellular tissue. This may give rise to a hard, lumpy mass of chronic inflammatory material of brawny character with ill-defined edges, or to multiple smooth nodules of uniformly firm consistence. One or more of the nodules may liquefy and discharge their characteristic granular and viscid necrotic contents. Healing of the sinuses may occur but is unusual while superadded infection persists.

Mode of Spread. Unlike syphilis and tuberculosis, which it resembles in some respects and with which it is sometimes confused, actinomycosis spreads directly through the tissues. It does not usually attack the lymph glands, probably because the organism is too big to be carried by the lymph vessels. The disease begins in the submucous or subcutaneous tissues and travels in the fibrous tissue planes of the body. Muscles are pushed aside or infiltrated. Invasion of a vein is uncommon, but spread by the blood stream may account for metastatic lesions. Death in actinomycosis may be due to involvement of vital structures, generalized pyæmia, or to amyloid disease.

ACTINOMYCOSIS AT SPECIAL SITES

Almost any organ of the body may be attacked by actinomycosis, but there are special sites at which it occurs. In over 60% of cases

the region of the jaws, tongue, pharynx, and neck is affected ; in about 20% the abdominal viscera ; and in the remainder the thoracic organs. Sometimes there are multiple foci in various parts of the body.

(1) **Tongue, Jaw, Pharynx and Neck.** A primary lesion in the tongue is rare ; it usually begins at the margin of the organ in the form of a small deep-seated painless nodule which grows slowly. As the nodule approaches the surface the mucous membrane becomes stretched, and yellow areas, corresponding to underlying abscesses, make their appearance. The condition in cattle known as "woody tongue" was formerly ascribed to actinomycosis but is due to a specific actino-bacillus.

In man the jaws are the commonest starting point of actinomycosis, and the lower jaw is affected much more often than the upper. The disease often begins close to the angle of the mandible, and is often related to a carious tooth or an abrasion. Trismus may be an early sign. The lesion involves the soft tissues surrounding the jaws, and the bone, protected by its periosteum, is not usually attacked directly, but the indurated tissues may be so fixed to the bone that an osseous origin of the disease may be suspected. The affected parts are firm and tough, diffusely swollen at first, and nodulated later. The disease spreads to the cheek and parotid gland and to the arcolar tissues of the neck, in which it extends rapidly. In the neck, unless they are deep seated, the lesions can be felt as firm nodules and the skin over them is often livid and puckered. As the nodules increase in size they soften to the degree of fluctuation and finally rupture, discharging sero-purulent fluid and greyish or yellow masses containing the ray fungus, and leading to the formation of sinuses, which may intercommunicate. The skin, usually infiltrated and board-like, varies in colour from pinkish-red to dusky-blue. The lymph glands are not involved unless there is a superadded infection.

From the neck the disease may extend to the mediastinum or to the vertebral column and the meninges. When the upper jaw is involved the disease may spread to the orbit or base of the skull and even to the brain.

(2) **Thoracic Organs.** Actinomycotic infection of the lungs is sometimes primary, but it is due most frequently to extension either from the mouth, pharynx, and neck, or from the abdomen. In both instances extension is by direct spread.

In a few cases primary pulmonary actinomycosis may be caused by direct aspiration of infective material from the upper respiratory tract ; and metastatic lesions through the blood stream are said to occur.

The pathological appearances vary greatly, and three main types of lesion, which represent different stages of the process, are described.

(1) The *bronchitic*, in which the infection is confined mainly to the large bronchi. (2) The *pneumonic*, in which the process spreads from the bronchi to the alveoli, which become filled with pus. (3) The *pleuro-pneumonic* in which the abscesses have burrowed to the pleural surface and produced empyema. Often a considerable attempt at healing by fibrous tissue is evident, so that hard, fibrous nodules alternate with typical softer lesions or abscesses. The chest wall is often involved,

and discharging sinuses may result. The brain may be involved by metastasis through the blood stream.

(8) **Abdominal Organs.** Primary abdominal actinomycosis accounts for about 20% of all cases. The ileocaecal region and the liver are most frequently attacked, less often the pelvic colon, and rarely the duodenum and the gall bladder.

The commonest starting point for actinomycosis is the ileocaecal region, due to sudden or gradual escape of infection from a diseased appendix.

The disease is usually insidious in onset and chronic in course. It may become very widespread, and involve many of the abdominal organs by extension in the retroperitoneal tissues. It may extend even into the thigh, and may involve the hip joint.

In a few cases abdominal actinomycosis has a sudden onset and may simulate appendicitis. At operation the appendix may be found to be involved in a mass of granulation tissue. When suppuration is present an indolent sinus may persist after operation, and become surrounded by vascular granulations and miliary abscesses. Sometimes at operation there is no palpable or visible mass, and the appendix appears healthy, and it is only subsequently, when the disease becomes more advanced and breaks through the wound, that its nature becomes obvious.

The liver is a fairly common site for actinomycosis. The lesion is sometimes a primary one, but more often is secondary to actinomycosis from the ileocaecal region or even from the lung. In cases in which no primary lesion is found in the intestine it is probable that the organism has reached a tributary of the portal vein through a small abrasion, or that the primary actinomycotic ulcer was small and has healed. The right lobe is the common site. It becomes enlarged and acquires adhesions with neighbouring structures. When cut the affected part has a very characteristic honeycomb appearance, probably due to coalescence of a group of abscesses; their contents have a rather bright yellow colour. Secondary infection of an actinomycotic abscess by pyogenic organisms is not unusual. Smaller abscesses may be present a short distance from the main one.

Actinomycosis of the liver may penetrate the diaphragm and infect the pleura and lung, or it may involve the abdominal wall, giving the skin a characteristic board-like hardness.

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CHAPTER VI

HYDATID DISEASE

HYDATID disease in man is caused by the *Echinococcus granulosus*. This is a cestode which normally completes its cycle of development in two hosts. In the *definitive host*—the dog—it takes the form of an intestinal tapeworm, the *tænia echinococcus*. This is a small worm, 3–6 mm. long, consisting of four segments (Fig. 12). Ova set free from its terminal segment are evacuated in the feces.

In the *intermediate host*—generally the sheep, less often the ox or pig—the ova derived from food contaminated by canine feces penetrate the intestinal tract and are carried to the liver, where they lead to the

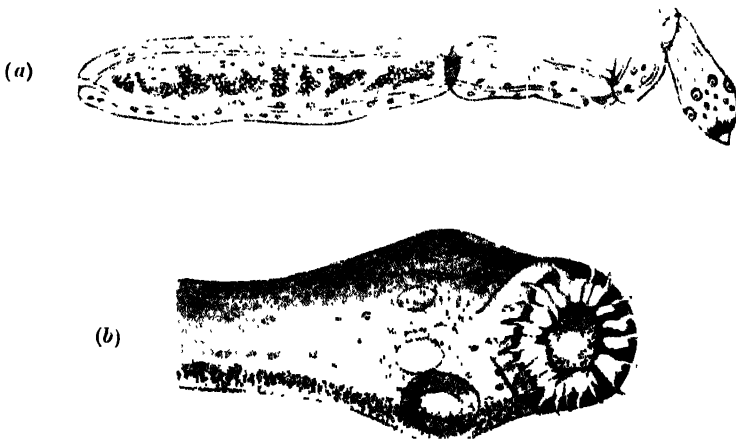


FIG. 12.

- (a) *Echinococcus granulosus*. Note the ova in the distal segment.
(b) Head of *Echinococcus granulosus* showing suckers and hooklets.

formation of a hydatid cyst. Less often, secondary hydatid cysts may arise in the lungs or other sites.

Man, like the sheep, acts as an intermediate host. Probably in most cases the infestation is acquired in childhood as a result of contact with an infested dog.

Geographical Distribution. The disease occurs in all countries; but it is found with greatest frequency in those in which sheep are pastured in large numbers, because these animals act as the intermediate hosts for the parasite. On this account Australia, New Zealand, the Argentine, and South Africa, which are the great sheep-raising centres of the world, show the highest incidence of the disease. In the State

of Victoria in Australia it has been estimated by Dew that 1 per 300 hospital admissions is on account of hydatid disease. In Europe, hydatid disease is rare, although there are a few countries, such as Denmark, Northern Italy, Bulgaria, and Iceland, where the disease has a relatively high incidence. In the British Isles only isolated cases occur, and most of them are in Orkney and Shetland.

Development of the Hydatid Cyst. The embryo usually lies in one of the liver lobules, where its presence sets up a very active cellular reaction. An infiltration of the tissues with lymphocytes and endo-

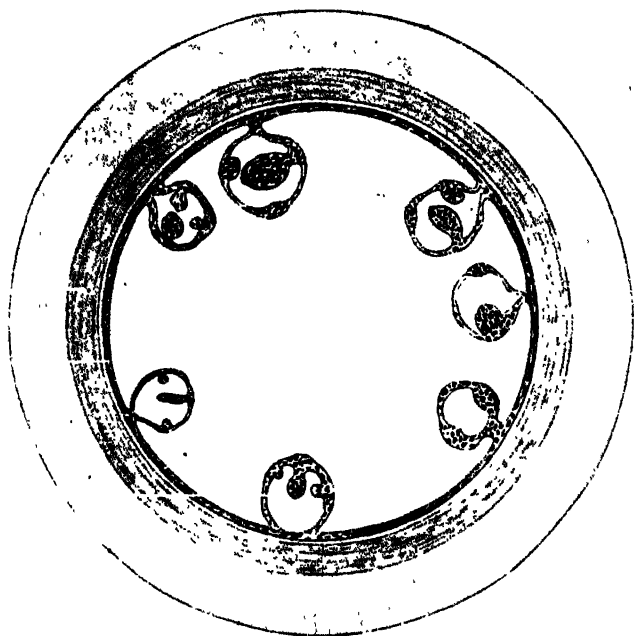


FIG. 13. Diagram of a fully developed unilocular hydatid cyst. *a*, adventitia or ectocyst; *b*, laminated membrane; *c*, germinal layer; *d*, brood capsule with scolices. (Modified from Dew.)

thelial cells as well as with erythrocytes occurs, and the specific response to the helminthic toxin is evidenced by eosinophilia.

About fourteen days after implantation the parasite assumes a vesicular form, and at this stage four zones may be observed; in the centre is the vesicular embryo, surrounded by a layer of endothelial cells, around which are concentrically arranged fibroblasts, and, at the periphery, a few layers of degenerated liver cells. By the fourth week the cyst is quite recognizable by the naked eye, and by the third month it may be several centimetres in diameter.

Structure of the Mature Cyst. The fully developed cyst is lined by a membrane, variously known as the *endocyst*, *granular*, *parenchymatous*, or *germinal layer*, composed of small nucleated masses embedded in granular protoplasm, from the inner aspect of which

project the *brood capsules and scolices* (see below). The lining membrane is very loosely attached to the subjacent *laminated layer*, which is firm and serves to protect the delicate germinal layer and its developing scolices. The laminated membrane is very impervious to noxious agents. The outer coat or *ectocyst* is an adventitious capsule formed from the tissues around the cyst, and is, therefore, not an integral part of the parasite. It is composed of fibrous tissue and varies greatly in thickness. There is a definite line of cleavage between the laminated layer and the adventitious capsule.

In the interior of the cyst is the characteristic hydatid fluid, clear, and opalescent with an alkaline reaction. It acts as a nutrient medium for the developing scolices.

Brood capsules develop from the germinal layer and appear as small vesicles attached loosely to its inner surface. Scolices develop on the surface of the brood capsule at several points by a process of evagination and cupping of the proliferating capsule. A typical scolex is attached to the brood capsule by a fine stalk and swings freely within the capsule. The mature scolex has the typical shape of the head of the mature worm and the same arrangement of hooklets, which have a retractile mechanism to protect them from contact with their neighbours.

A daughter cyst is a replica of the mother or primary cyst within which it occurs. It generally develops when the vitality of the mother cyst is endangered, and thus represents a defensive mechanism for the larval cestode. Daughter-cyst formation may follow injury, infection, or the entry of noxious fluids into the cyst; but is rarely observed in childhood, or in cysts in such sheltered sites as the brain and bones.

PATHOLOGICAL FEATURES OF HYDATID CYSTS

Hydatid cysts have been observed in almost every organ of the body, but the majority, as mentioned above, occur in the liver or lungs.

The rate of growth of a cyst is very variable and depends on the tissue in which the cyst occurs. In soft vascular organs like the lung, spleen and brain, cysts grow rapidly compared with cysts within the bones. The parasite may retain its vitality for as long as 40 years, or it may die spontaneously or as a result of rupture or infection of the cyst. In the early stages of its growth it usually gives rise to eosinophilia, and this may recur if rupture, leakage or infection of the cyst takes place. If the parasite dies the cyst wall may become calcified and the contents pultaceous (*atheromatous cyst*).

As the fluid of a hydatid cyst is under considerable pressure, the cyst remains spherical, and tends to grow in the lines of least resistance. Thus a cyst of the liver may become pedunculated, or may bulge into the retroperitoneal tissues.

As a hydatid cyst grows but slowly, pressure effects may be long deferred, for the affected structures have sufficient time to accommodate themselves. In the liver the costal margin may bulge, or the bile ducts may be occluded. In the brain, signs of increased intracranial pressure may become evident.

In operations upon hydatid cysts, advantage is taken of the lack of cohesion between the laminated layer and the adventitious capsule to enucleate the cyst. To eliminate the risk of disseminating the disease, the contents of the cyst are usually destroyed by injection of formalin. Excision of the cyst is unnecessary, although removal may conveniently be carried out if the cyst be pedunculated.

Hydatid Anaphylaxis. Rupture or leakage of a hydatid cyst may occur spontaneously or as a result of puncture or other surgical interference. After rupture, especially if the patient has previously been sensitized by minor leakage from the cyst, anaphylactic phenomena, mild or severe, may occur. For this reason exploratory puncture of a cyst is a particularly injudicious practice.

The anaphylactic phenomena vary from pruritus and urticaria or a feeling of constriction in the chest, to serious symptoms such as convulsions, pulmonary œdema or syncope. General anæsthesia mitigates the effects of anaphylaxis, but their manifestations may be delayed until after recovery from the anæsthetic. The sensitization resulting from repeated absorption of protein from hydatid fluid is utilized for two diagnostic measures, the complement-fixation test and the intradermal reaction (of Casoni).

HYDATID CYSTS IN SPECIAL SITES

(1) **Liver.** As the ova of the *tænia echinococcus* are conveyed by the portal circulation it is not surprising that at least 75% of all hydatid cysts affect the liver, and when hydatids are present in other organs, such as the lungs, the liver is affected in about 50% of cases. This is a consideration of great importance in prognosis and treatment.

In the liver hydatid cysts tend to develop in young subjects, though they often remain latent. The right lobe is more commonly affected than the left in the proportion of about 4 : 1, and when the cysts grow to large size the unaffected lobe usually shows considerable compensatory hypertrophy. Cysts near the peritoneal surface of the liver tend to spread towards the abdominal cavity, those originating near the free border of the liver may become pedunculated. At the superior surface of the liver the cyst may cause elevation of the diaphragm, a feature recognizable by radioscopy. A cyst occasionally originates at the bare area of the liver, and may then extend into the retroperitoneal tissues.

In adults, daughter cysts are present in fully 90% of cases as a result of irritation caused by the entry of bile from the finer bile ducts in relation to its walls.

The majority of hydatid cysts in the liver remain latent. Ultimately the parasite dies and the cyst wall undergoes calcification. In a small proportion of cases complications occur, of which the chief are (a) suppuration, and (b) rupture.

(a) In a univesicular cyst the laminated layer is impermeable to organisms, therefore suppuration only occurs after communication with the bile passages. The common infecting organisms are bacillus coli, streptococci, and staphylococci, but sometimes gas-producing organisms are present.

(b) The cyst may rupture into the biliary passages, the peritoneum, the pleura and lung, or rarely into an abdominal viscus.

If the cyst ruptures into the biliary passages, obstructive jaundice may result, or daughter cysts may be discharged and may be discovered in the stools. Rupture into the peritoneal cavity may give rise to severe anaphylaxis, and later to the development of multiple



FIG. 14. Hydatid cyst of the kidney causing hydronephrosis.

(Museum of Royal College of Surgeons of Edinburgh.)

daughter cysts. In some cases the rupture leads to extravasation of bile and to an early fatal issue.

Rupture into the thoracic cavity is usually a complication of suppuration of a large cyst, especially one situated in the upper part of the liver, on the right side. Empyema is the natural result, but sometimes rupture occurs directly into the lung which has become adherent to the suppurating cyst. As a result the contents of the cyst may be expelled into a bronchus.

Rupture of a hydatid cyst into the stomach, the small intestine,

and the colon has been recorded. Such complications are rare and are usually sequelæ of suppuration.

(2) **Lungs.** After the liver, the lungs are the commonest site of echinococcal cysts, and the possibility that a pulmonary and a hepatic cyst may coexist should not be overlooked. The usual route by which the parasite reaches the lungs is by the blood stream *via* the liver.

The right lung is affected twice as often as the left, and the lower lobe is the common site. As a rule the cyst arises near the surface of the lung (peripheral cyst), much less often near the hilum (para-bronchial cyst). Occasionally the cysts are multiple.

The lung tissue is non-resistant and therefore pulmonary cysts grow relatively quickly and daughter cysts are not present until a late stage. The laminated membrane and the adventitious capsule are usually very thin, especially while the cyst is univesicular and uncomplicated. Brood capsules with scolices are almost always present.

A peripheral cyst is usually attached to the parietal pleura by light adhesion, which following infection may become firm and widespread. A pulmonary cyst may rupture into a bronchus or into the pleural cavity, or it may become infected and lead to abscess formation in the lung or to pyopneumothorax. Rupture into a bronchus is a common event, and albuminous fluid, or the membrane of daughter cysts, may be expectorated, and natural cure may follow.

(3) **Brain.** Hydatid cysts in the brain are rare. The cyst is single and unilocular; it is seldom larger than a hen's egg and its adventitious capsule is very thin. Any part of the brain may be affected, but the commonest site is one of the cerebral hemispheres superficially. The cerebellum is rarely involved. In children the skull bones may bulge over the surface of the cyst, but in adults they are more rigid and merely show thinning at the point of contact of the cyst. The cyst may deform, and finally rupture into the ventricles of the brain.

In the brain a hydatid cyst grows very slowly, and is therefore for long symptomless. The effects produced by the cyst vary according to its situation and are similar to those caused by benign tumour. A single cyst is readily amenable to surgical removal.

(4) **Kidney.** Even in places where hydatid disease is common, renal hydatid cysts are rare, and when they occur seldom produce very definite signs. They may reach an enormous size without producing any important complication. Occasionally the cyst ruptures into the renal pelvis and may then become infected. Hydatid membrane, or even daughter cysts, may be passed in the urine, with symptoms of ureteral colic or urethral obstruction.

(5) **Bone.** This is one of the rarest sites for hydatid disease. The bones which have been most often attacked are the humerus, the femur, the vertebræ, the tibia, and the innominate bone. As hydatids in bone grow very slowly, they are usually recognized only in adults.

The signs and symptoms of hydatid disease are modified on account of the resistant nature of bone which inhibits actual cyst formation, and results in solid masses of hyaline material, like grains of boiled sago.

At the seat of disease the affected bone is expanded in a globular

or fusiform fashion. The osseous tissue slowly disappears, and is replaced by hydatid elements. So slow is this process that none of the conditions for reformation of bone is provoked.

The outstanding feature of hydatid cysts in bone is their extreme latency. In situations like the femur or humerus, spontaneous fracture is often the first indication of the affection. Such pathological fracture is a grave complication, not so much on account of the improbability of union, but because it leads to dissemination of the disease in the soft tissues. Radiographically, hydatid disease in bone may be almost indistinguishable from osteitis fibrosa.

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CHAPTER VII

TUMOURS

TUMOUR formation, its nature and causes, its relationship to other diseases, its prevention, control and treatment, are problems of great perplexity, which have in turn attracted and baffled all who have studied them. The problem of new growth holds many disappointments for those who attempt to probe its mysteries, and many forsake it for more promising fields of study, but nevertheless it remains one of the most fascinating subjects in the whole realm of pathology.

Powell White has defined a tumour as "a mass of cells, tissues or organs, resembling those normally present in the body, but arranged atypically, which grow at the expense of the organism, without, at the same time, subserving any useful purpose therein." The most striking attribute of all tumours is their complete autonomy. A tumour is derived from the cells of the body in which it grows; it is as much an integral portion of the body as the liver or kidney or any other organ, yet it recognizes no laws except its own, proceeds independently, and often encompasses the destruction of its host.

The autonomy of a tumour is clearly demonstrated by the manner in which it exacts nourishment regardless of the state of nutrition of the victim. It is like a mutinous army devastating its own country, for, however impoverished the host becomes, the tumour continues to flourish.

One of the few favourable features of even the most malignant tumours is their local origin, and it is upon this that the whole treatment of cancer by surgery is founded. It is probably not true that a tumour always starts from a single atavistic cell—in the breast, for instance, the origin is probably multicentric—but nevertheless it is correct to assume that in the majority of cases a tumour at its inception is localized. Simple tumours remain localized indefinitely, and many malignant tumours remain so for a period measured in months or years. A few, however, such as certain types of melanoma, spread rapidly to other parts, so that secondary nodules may appear even before the primary growth is recognized. In other cases, multiple primary malignant growths may appear, simultaneously or in succession. They may occur in different parts of the same organ, in paired organs, or in different parts of the body.

SIMPLE AND MALIGNANT TUMOURS

Between typical simple and malignant tumours there is little in common except their autonomy, and the distinction can usually be made with ease on either clinical or pathological examination. Other tumours, however, possess some of the features of both classes, and are

not easily assigned to one or other, whilst yet other tumours change their nature in the course of years, and, after a period of simple growth, undergo malignant change.

The distinction between simple and malignant tumours is consequently not always possible, but in general it can usually be settled by the following criteria :—

(1) A simple tumour usually attains a limitation of growth, and after reaching a certain size ceases to progress or at least progresses more slowly. A malignant tumour, on the other hand, grows continuously, and, even when it has impoverished its host and source of nutrition, it still retains the potentiality for further proliferation if adequately nourished.

Illimitable growth is seen in malignant mouse tumours which, if suitably transplanted from animal to animal, continue to live and grow long after their first host is dead. Jensen's mouse tumour arose



FIG. 15. Pericanalicular fibro-adenoma of the breast, removed from a woman aged twenty-eight years. The tumour had grown slowly during several years. It is non-malignant, and is surrounded by a well-defined capsule of condensed fibrous tissue.

(Department of Surgery, University of Edinburgh.)

spontaneously in a white mouse in the year 1900, has since been conveyed from mouse to mouse in many laboratories throughout the world, has produced during that time innumerable large tumours which together must be many million times the weight of the original mouse, and thirty years later (ten times the mouse's span of life) was still growing actively.

(2) Usually a malignant tumour grows rapidly, a simple one slowly. To this, however, there are many exceptions; some simple tumours grow more quickly than cancers, and few malignant ones grow more quickly than that most innocent of "tumours," the foetus.

(3) Malignant tumours invade and destroy neighbouring tissues and possess no effective capsule: simple tumours merely expand, and consequently are sometimes encapsuled. The glioma, however, has no capsule, though in the pathological sense it may be non-malignant, and there are other exceptions to this general rule.

(4) Malignant tumours readily ulcerate upon free surfaces, by invading the surface membrane and interrupting its blood supply: simple growths rarely ulcerate unless they undergo necrosis or suppuration.

(5) Malignant tumours tend sooner or later to disseminate and form metastases, and unless treated early and radically they almost invariably kill : simple tumours rarely cause fatality unless they interfere with the function of vital organs.

Microscopic Appearance. Microscopically, the nature and degree of malignancy of a tumour may be judged on three distinct criteria : (1) the relation of the tumour to its environment, (2) the structure of the tumour, and (3) the appearance of its cells. In general, the first criterion is most valuable, and for this reason it is important to examine the growing margin rather than the central parts. The most obvious evidence at the growing margin is the presence or absence of invasion of surrounding tissues, for with few exceptions malignant growths invade, simple ones do not.

In regard to internal structure of tumours, the striking feature is that simple tumours tend to repeat with some degree of accuracy the

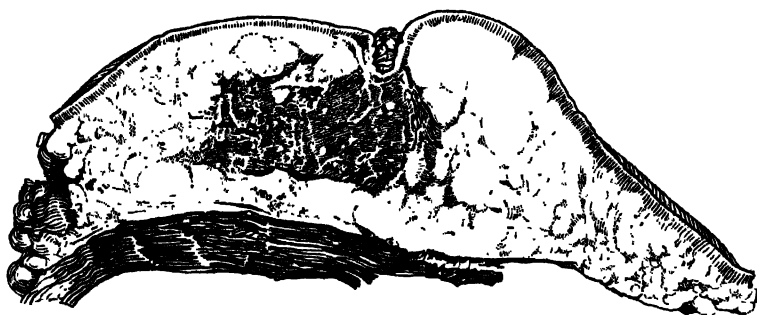


FIG. 16. Scirrhus carcinoma of the breast. The tumour possesses no capsule and has infiltrated the tissues of the breast. The nipple is deeply retracted.

(Department of Surgery, University of Edinburgh.)

pattern of the tissue from which they are derived, whereas malignant tumours reproduce the tissue very imperfectly or not at all.

The appearance of the individual cell of a simple tumour may be hardly distinguishable from the normal, but in typical malignant growths the cells have several strikingly abnormal features. In general, the malignant cell may be said to possess anaplastic characters and to approximate to an embryonic type. The principal function of an adult cell is to work, that of the embryonic cell is to multiply, and the more malignant the cell the more does it develop the latter function at the expense of the former. Typically, a malignant cell is larger than its prototype, is of irregular shape, and stains more deeply. The nucleus, which is a reliable guide to the state of activity of the cell, is hyperchromatic, and often of vesicular appearance. Mitotic figures are common in rapidly growing tumours, and often the mitosis is of irregular pattern. Sometimes there is a large densely staining spot quite distinct from the nucleus, the so-called "bird's eye spot." These spots have often been regarded as parasitic inclusions, but they are probably due to multiplication of the centrosomes in irregular cell-division. Another

index of rapid growth is the presence of "tumour giant cells," which must not be confused with other types of giant cell, such as occur in specific forms of tumour or around foreign bodies (see Fig. 71).

GRADES OF MALIGNANCY

Attempts have been made to assess and grade the degree of malignancy of tumours according to their cytological pattern. Such an index of malignancy was formulated by Broders and was at one time adopted freely in America.

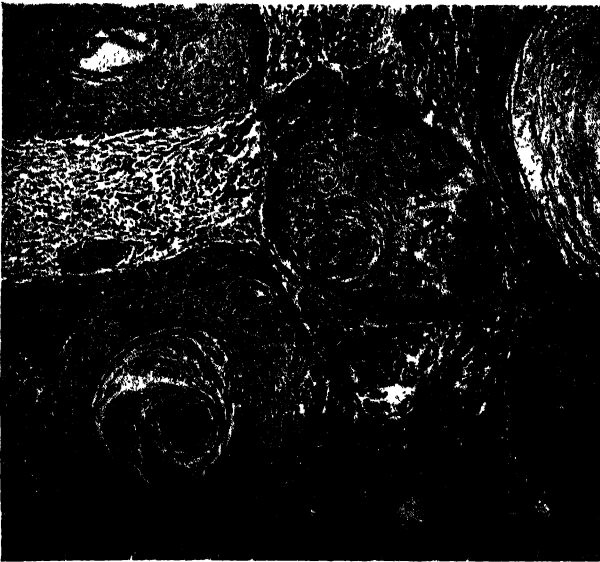


FIG. 17. Squamous-cell carcinoma (epithelioma) of the tongue. $\times 70$. The cells are highly differentiated, and some are keratinized and have given rise to cell-nest formation. This tumour would correspond to type 1 of Broders' classification. Note the lymphocyte infiltration near the lower margin of the section, a common feature in lingual carcinoma.

This method differs from most others in that it relies entirely upon the microscopic appearance of individual cells of a tumour, and upon the degree of "de-differentiation" or reversion to the embryonic type displayed. Four grades of malignancy are recognized. If 75% or more of the cells are highly differentiated, the tumour is assigned to Group 1, the group of lowest malignancy. Group 2 contains those tumours with 50% to 75% of the cells differentiated, Group 3 with 25% to 50%. In Group 4 are those tumours in which the majority of the cells are "de-differentiated," and consequently includes the most malignant types.

Broders' method appears to be helpful when applied to such

growths as squamous-cell carcinoma of the skin, tongue and lip, and should not be regarded as generally applicable to all tumours. In assessing the malignancy of a tumour there are, of course, many other factors to be taken into account besides its histological grading. Such

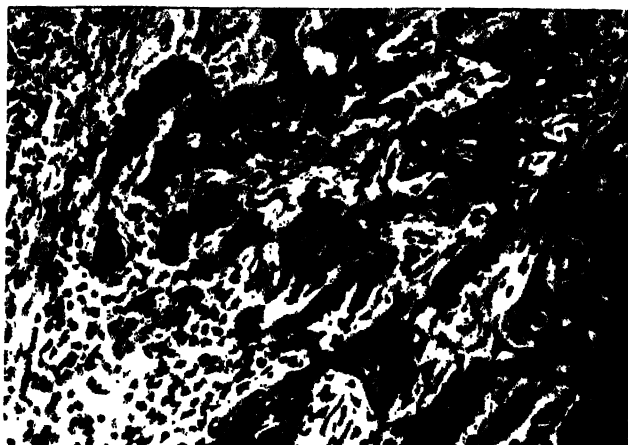


FIG. 18. Squamous epithelioma of invasive type without keratinization or cell nest formation. This tumour would correspond to type 4 of Broders' classification.

(Department of Pathology, University of Glasgow.)

features as the size and extent of the tumour, its position in relation to lymph drainage, its accessibility for surgical eradication, and its radio-sensitivity, may all have to be considered.

SPREAD OF MALIGNANT TUMOURS

Since the object of surgical operation in malignant disease is to extirpate all invaded tissues, the study of all the possible routes by which tumours spread is of immense practical importance. Indeed, the influence of such considerations upon the scope of the operative treatment is manifest in every region of the body.

A sarcoma differs from carcinoma in its method of extension. It infiltrates locally in much the same way, but sarcoma shows a great tendency to early dissemination by the blood stream; whereas carcinoma spreads first and principally along the lymph channels, and gives rise to blood-borne metastatic deposits at a relatively late stage or not at all.

The spread of carcinoma, which is of greater surgical importance than sarcoma, will be considered in more detail. Carcinoma may spread in the following ways :—

- (1) Invasion of adjacent tissues.
- (2) Permeation and embolism in lymph channels.
- (3) Embolism by the blood stream.
- (4) Implantation of free cells.

(1) **Invasion.** Direct invasion of surrounding tissues is always the first mode of spread. Indeed, it is often difficult to assume that a tumour is malignant until it invades.

As the tumour invades it destroys the surrounding healthy tissues, probably in virtue of enzymes from the malignant cells.

A tumour does not invade uniformly, but its invasion is influenced to some extent by the disposition of fascial planes and other barriers. It seems that the invading cells take the paths of least resistance, and any tough membrane, especially if avascular, exerts a restraining influence. The pylorus forms a most remarkable barrier to the spread of tumours, and is rarely transgressed even by the most malignant gastric carcinoma.

Carcinoma, like sarcoma, extends principally in connective tissues, but carcinoma may invade epithelial structures such as the skin and mucous membranes. For this reason a carcinoma, if superficial, commonly ulcerates early.

(2) **Extension by Lymph Vessels.** Extension by lymph vessels often occurs early in carcinoma, and it provides the great obstacle to eradication of the disease by operation. There are two possible modes of spread within the lymph vascular system: (a) by permeation, (b) by embolism.

Sampson Handley has vigorously sponsored the theory of permeation. According to him, the tumour, having once gained access to the lymph vessels, grows centrifugally in all directions in the form of advancing columns of cells, which permeate further and further from the primary growth. As the malignant cells at the head of each advancing column divide and progress the cells further back become obliterated by a fibrous peri-lymphangitis. Consequently a centrifugal zone of spread, a "malignant ring-worm," results, which increases progressively and reaches more distant parts of the body. At intervals some of the cells of this annular zone grow more actively and form visible metastases. Hence, in such a region as the breast, the earliest metastases usually lie close to the primary tumour, whereas those formed later lie at progressively greater distances.

In support of this view Sampson Handley has put forward many interesting observations, most of which relate to cancer of the breast, and are considered more fully in the chapter on that subject. The theory has not yet, however, received complete acceptance. Most authorities agree that spread by permeation does occur, but few are prepared to attribute to this process the predominant rôle that Handley claims for it.

Of the second process of lymph spread, cell embolism, there is no doubt. Small groups of cells set free in the lymph vessels are carried by the gentle lymph current to neighbouring glands, where they are arrested in the subcapsular sinuses. By such a process glands comparatively remote from the primary tumour may be involved at an early stage, and successful operation thus precluded. Conversely, carcinoma arising in tissues of which the lymph drainage is impaired by previous lymphangitis does not metastasize for months or even for

years. (Lupus carcinoma, for example, rarely metastasizes until the primary growth has extended beyond the area of lupus and has thus reached patent lymph channels.)

(3) **Dissemination by the Blood Stream.** This usually occurs late in carcinoma, although there are exceptions. The lateness is partly due to the fact that in carcinoma the blood vessels are well developed and are not easily invaded by tumour cells, and partly to the fact that carcinoma cells which have reached the blood stream and have been deported to distant sites do not necessarily survive. Schmidt has shown that the lungs may contain many cancerous emboli, which have failed to engraft, and instead lie buried in fibrous capsules inside occluded blood vessels.

Blood-borne metastases show a remarkable affinity for certain organs or tissues. The lungs, liver, brain and bones are commonly affected, whereas the muscles, heart and spleen are almost exempt. Some tumours commonly give rise to metastases in the liver and lungs; others, *e.g.* (tumours of the breast, the kidney and the prostate, often metastasize to bones.) These facts clearly indicate that the tissues differ in their susceptibility to cancerous invasion.

Malignant emboli from almost any part of the body are first arrested in the capillaries of either the liver or the lungs, and consequently the first blood-borne metastases are usually in these organs. Occasionally, however, metastases arise in other regions without the lungs or the liver being obviously involved. According to Schmidt, malignant cells held up in the lungs, though unable to form pulmonary metastases, may proliferate along the pulmonary capillaries and reach the venules, and so may escape into the systemic circulation.

(4) **Implantation of Free Cells.** This mode of dissemination is seen most clearly in the peritoneal cavity. Cells from a tumour of the stomach, colon or other viscus may be set free and engraft on other parts of the peritoneum. The ovaries are commonly involved in secondary growths by this method (*see* p. 709). Implantation of free cells is believed to play a part in the spread of tumours in the renal pelvis, the ureter and the bladder. A papilloma of the bladder commonly gives rise to companion growths in this way, and a papilloma of the renal pelvis may lead to secondary masses in both the ureter and the bladder.

Another instance of implantation of free malignant cells is that which occurs at operation. It is especially apt to result from incision of a tumour, as at biopsy, but it may occur whenever incomplete removal is carried out. There is no doubt that malignant cells are set free in a considerable proportion of incomplete operations, but actual implantation and growth is comparatively uncommon. "Recurrence" of carcinoma more often takes the form of a distant metastasis than of a secondary nodule at the site of operation.

INCIDENCE OF TUMOURS

Age Incidence. The varying age incidence of different tumours and of tumours in different regions is, of course, well recognized. A

sarcoma usually arises in adolescence or in early adult life, carcinomata at a later age, though to this generalization there are many exceptions. The tendency to carcinoma becomes evident after the age of forty years and increases with advancing years; it is greatest in old age, but owing to the lower figures of total population in later decades most cases of cancer occur before the age of sixty years. Tumours in different sites show astonishing age variations: adrenal neurocytoma occurs characteristically in infancy, cerebellar glioma in childhood, bone sarcoma between the ages of fifteen and twenty-five years, post-cricoid cancer in the thirties, cancer of the prostate in old age; and the list could be multiplied time and again. In many cases, as in tumours of such organs as the breast, prostate and ovary, the reason is possibly to be found in the cycles of functional activity of the part; in other cases no explanation is yet apparent.

Sex Incidence. There are some noteworthy features concerning the sex incidence of tumours. Cancer of the breast and uterus have, of course, no counterpart in males, and for the greater part are related to the sexual functions or malfunctions of these organs, but the sex incidence of tumours varies in other parts of the body not connected with reproduction. Such sex divergences are common in the upper alimentary tract. Post-cricoid cancer is found in women—comparatively young women—in 90% of cases. Cancer of the lower part of the œsophagus occurs principally in middle-aged or elderly men, as does cancer of the stomach. In some regions the sex incidence can be explained by the habits of one sex or the other, as in most occupational cancers, and in cancers of the oral cavity, which are sometimes associated with pipe-smoking and with syphilis; but in other regions no predisposing factors can be found.

There are some interesting statistical features in relation to cancer of the breast, the uterus and the ovary. Cancer of the neck of the uterus usually occurs in parous women, but, as Deelman and others have shown, it is little more common in multiparæ than uniparæ. It would seem that the first confinement alone is responsible for the susceptibility to malignant change, and there is much evidence to show that the most important of these factors are laceration of the cervix during delivery and resulting cervical catarrh.

Cancers of the breast and the ovary, on the other hand, are common in nulliparous women. Possibly this is because they depend on some malfunction arising from lack of full physiological stimuli.

Racial Incidence. The racial incidence of cancer has not yet been investigated upon a statistical basis sufficiently complete for definite conclusions, but there is at least evidence that cancer is known throughout the world and is common in every race. From time to time cancer is attributed to the influence of civilization, to desertion of the "natural mode of life," and even to specific habits thought to be limited to civilized peoples, but, in general, each of these views is without scientific corroboration.

Curious differences do exist, however, in the racial incidence of certain forms of cancer. This has been most clearly established for Holland and Great Britain. It is found that in Holland the incidence of

cancer of the breast is much lower than in Great Britain, but as though to compensate for this the Dutch women are more liable to growths in the alimentary tract. Statisticians are at a loss to account for these divergences in the absence of such factors as variations in diagnostic efficiency or differences in methods of compilation. As Greenwood points out, it will be interesting to note if similar differences obtain in various nationals living under comparable conditions in such a country as the United States of America.

ALLEGED INCREASE OF CANCER

It is undisputed that in most civilized countries during the past half-century there has been a great increase in the recorded number of deaths from cancer, but in spite of this there is no complete proof that cancer in general is on the increase. There are many obvious fallacies in drawing conclusions from the simple death rate, and of these the most important is that which arises from the ageing of the population due to improvements in public health and in the treatment of other diseases. The general population contains a far larger proportion of persons over forty years of age than it did a few decades ago, and the frequency of cancer is correspondingly greater.

In addition, there have been great improvements in the diagnosis and the recognition of cancer. Radiography, cystoscopy, and other diagnostic methods, together with a readier recourse to exploratory operation, have revealed many unsuspected new-growths; and routine microscopic examination has shown that many apparently simple lesions, *e.g.*, in the prostate or ovary, are actually neoplastic.

If allowance is made for ageing of the population it is found that the greater part of the alleged increase of cancer is referable to growths in inaccessible regions, whereas cancer of the skin, the mouth, and the neck of the uterus show little increase in frequency. For these and other reasons the balance of informed opinion inclines to the view that cancer in general has suffered no disproportionate increase. Exceptions, are, however, to be found in isolated types of cancer. Dunlop has shown that in Scotland there has been an absolute increase in the death rate from cancer of the breast, and since in death from this disease the cause can hardly fail to be recognized the incidence cannot be attributed to better diagnosis. Certain occupational cancers are undoubtedly on the increase, but this is in most cases clearly attributable to industrial conditions (*see* p. 69). It is almost certain that cancer of the lung is more common now than formerly, but the cause is unknown (*see* p. 347).

HEREDITY AND CANCER

This is one of the most controversial subjects in the whole field of cancer, and medical opinion on it is diverse and even contradictory. General statistics based on deaths from cancer are almost valueless, for quite apart from the inaccuracies of death certification the human

stock is so mixed that satisfactory evidence for or against an hereditary basis would require full pedigrees, complete with medical histories, dating back for many generations.

Most physicians of long experience must have met with families with apparently a strong disposition to cancer, and medical literature contains many such records. One of the most famous is that described by Broca, in which sixteen members of a family of twenty-six died from cancer of the breast, liver or uterus; and Warthin has related equally striking examples. On the other hand, it is pointed out that even such remarkable figures may be explained on a basis of coincidence, for cancer is so common in man—in Great Britain it kills fully 10% of those who reach the age of thirty-five—that any statistical evidence to be significant must deal with very large series of cases.

In the experimental laboratory, however, these statistical fallacies may be eliminated, for with such a fertile, short-lived, and conveniently small animal as the mouse it is possible to observe immense numbers of individuals whose pedigrees are known for many generations; and, moreover, by selective breeding the pedigrees may be so controlled as to eliminate many of the variables that confuse the issue in man. In this field the work of Maud Slye stands unparalleled in magnitude and result. Many thousands of mice have been bred under strict conditions of mating, and every mouse has been subjected to detailed post-mortem examination. In the first 30,000 autopsies there were 4,000 primary spontaneous tumours. Mammary carcinoma was by far the most common, but tumours of the lung and liver were not infrequent and there were many other types of simple and malignant growth.

By selective breeding, Slye has produced remarkable results, for by the continued inbreeding of mice of cancer-bearing ancestry, she has produced strains of which every individual attaining maturity dies of cancer, and by inbreeding cancer-free mice she has produced strains that appear completely immune to cancer. She has, moreover, shown that the tendency to tumours of specific type or in specific organs is also hereditary. Some strains of mouse were liable to adenoma, others to carcinoma or to sarcoma; some were liable to tumours of the liver, others to tumours of the lung or of the breast. From these and other experiments, Slye concluded that the tendency to cancer is hereditary, that cancer behaves as a unit character and that it is inherited as a Mendelian recessive.

All Slye's conclusions are not accepted by other geneticists, particularly in regard to the Mendelian relationship—some regard it as dominant, others as involving multiple factors—but there seems no doubt about the main thesis, the hereditary factor in cancer. It is not true to say that cancer itself is inheritable, but there is some hereditary disposition or diathesis which readily leads to cancer. Cockayne has recently reviewed Slye's work from this aspect. He concludes that the incidence of Slye's tumours depends upon some growth disorder such as adenomatosis, which is common in the three situations especially liable to cancer, namely, the lung, liver and breast. In the first two structures this factor probably behaves as a Mendelian recessive, in the

last as a dominant. Cockayne also cites interesting examples in man of cancers dependent upon similar hereditary predispositions. An outstanding example is cancer of the colon, which often shows a remarkable familial incidence. In some of these cases the cancer is related to the condition of polyposis of the colon, an hereditary disorder of cell growth which behaves as a Mendelian dominant. Another example is neurofibromatosis, a Mendelian dominant which sometimes leads to malignant change; and a third is the common pigmented mole, which may dispose to the formation of a malignant melanoma. Many more such hereditary predisposing factors will no doubt be defined by further studies in genetics.

TRANSPLANTABLE TUMOURS IN ANIMALS

When Jensen in 1903 published the results of his work on the propagation of mouse tumours he set the corner stone for a vast edifice of experimental tumour research, the results of which cannot fail to be of immense value in the general attack on the cancer problem.

Jensen's mouse tumour was a carcinoma, which occurred spontaneously in an elderly white mouse. By following the technique of previous workers he was able to transplant the tumour into other mice, and since then it has been transferred by grafting to millions more mice in laboratories throughout the world. At first the tumour only "took" in a small percentage of experiments, and principally in mice of the same breed; German mice, London mice, and wild mice of any origin were more resistant. In the course of time, however, the tumour adapted itself to these new hosts and eventually grew equally well in any variety of mice.

Jensen's work stimulated great interest in the study of animal tumours. Contrary to general belief at that time, it was found that cancer is not exclusively a human disease, but occurs widely in many vertebrates, and in amphibians, birds and fishes as well as mammals. It is particularly common in mice, and since they are convenient animals for laboratory study their tumours have been investigated most thoroughly.

It was soon found that tumour propagation is quite different from the transmission of any other disease. A tumour can only be propagated (except in the case of certain chicken growths which may not be strictly comparable) by the inoculation of living tumour cells, and all kinds of cell-free extract or culture are innocuous. Moreover, tumour propagation is mere grafting. The new tumour cells are derived from the original host only, and each later host merely acts as a sort of living culture medium whose function is to supply nourishment. When a carcinoma is transplanted its epithelial cells, or a small proportion of them, survive and proliferate, and they exact from their new environment a stroma with supporting tissue and blood vessels. Only very rarely do the cells of the new host become in turn malignant.

One of the most striking facts that has emerged from these studies

is that in spite of the wide zoological distribution of cancer, and in spite of the great similarity of many growths in different kinds of animal, the transmissibility of cancer has very strict limitations in regard to species. A mouse tumour cannot be propagated to rabbits, a human tumour never "takes" in the lower animals. It is true that heterologous transplants have succeeded in certain special situations, as in the brain of rats or of guinea pigs and in chicken embryos, but apart from these few instances tumours can only be grafted in very closely related species. Another remarkable feature is the way in which a tumour runs true to type throughout its whole course. (An adeno-carcinoma remains an adeno-carcinoma) and the very appearance of the cells may remain unchanged, as in the tumour described by Cramer, in which for fifteen years the cells retained their special property of storing glycogen. These are almost unsurmountable obstacles to a simple parasitic theory of cancer, for they would seem to postulate a separate strain of organism for each type of growth, as well as separate strains for each animal species.

Chicken Tumours. In recent years many studies have been made on certain chicken tumours. The best known of these, chicken tumour No. 1, described by Peyton Rous in 1911, was a spindle-cell fibrosarcoma, but since then several other types, all of connective-tissue origin, have been studied. The chief characteristic of most of them is that they may be transmitted from bird to bird by means of cell-free extracts as well as by living cells. In this respect they differ fundamentally from all known mammalian tumours, and for this reason many pathologists will not class them as true tumours but rather as infective granulomata resulting from unknown ultramicroscopic organisms.

It has been shown recently, however, that chicken tumours produced by the injection of tar extracts, which are undoubtedly true neoplasms, are also transmissible by means of cell-free filtrates. This would seem to indicate that filtrability is a chicken characteristic rather than a property possessed by the individual tumours, and it lends strong support to the view that experimental observations made upon chicken tumours may be applied to the problem of cancer in man.

EXPERIMENTAL PRODUCTION OF CANCER

It has already been related how, early in this century, the attention of experimental workers was turned to transplantable tumours in animals. Cancer research took another forward step with the discovery by Fibiger in 1913 and by Yamagiwa and Ichikawa in 1915 that cancer could be produced experimentally in animals.

Fibiger's brilliant study took origin from the examination of a spontaneous gastric carcinoma in a rat. In microscopic sections of the tumour he discovered the remains of a nematode worm, which he identified as a parasite found in certain varieties of Danish cockroach. Further investigation disclosed a source of infected cockroaches in a local sugar factory. Fibiger then fed a number of rats on a diet of the

cockroaches, and examined the stomachs of the rats at various intervals afterwards. In a short time after the start of the experiment the gastric mucosa developed signs of inflammatory reaction; this was followed by papillomatous proliferation, and later, sometimes within three months,

by actual cancer, which invaded adjacent tissues and gave rise to metastatic deposits. Nematodes could be found in the primary gastric tumour but not in the metastases, a significant observation which indicates that once the gastric cells had acquired malignancy they continued to proliferate in virtue of their own intrinsic energy.

Fibiger's work naturally aroused great enthusiasm for the parasitic conception of cancer, but with isolated exceptions there has been no evidence that other parasites behave like that particular nematode, nor can that nematode produce cancer except in the rat.

Recently, Passey and Leese have repeated Fibiger's experiments, but have failed to confirm his findings. According to these workers, Fibiger's results were due, in part at least, to the fact that the rats used in his experiments were kept on a diet very deficient in vitamins, a state which is well known to produce papillomatous proliferation in the lining membrane of the fore-stomach.

The next method of experimental cancer production, discovered by Yamagiwa and Ichikawa, was of a different nature. It consisted in subjecting the skin surface to prolonged and repeated application of coal tar. Rabbits were first used for

this purpose, and the tar was applied to the delicate skin on the dorsum of the ear. Later it was found that mice are much more susceptible, and that other substances than coal tar, *e.g.*, paraffin and shale oils, have similar effects.

When mice are painted twice or thrice weekly they develop first a



FIG. 19. Carcinoma of the colon associated with polyposis. The tumour is of annular type and has caused extreme stenosis of the bowel. There are several pedunculated polypi of typical appearance in the dilated bowel proximal to the tumour.

thickening of the epidermis with warty or papillomatous growths, and these are later followed by the formation of a carcinoma, which invades, ulcerates and produces metastases. In most cases the carcinoma appears after about six months, but occasionally in as short a time as three months or in some cases only after an interval of eighteen months. If the tarring is carried out less frequently the tumour takes longer to appear, and the percentage of successful results is smaller. It is interesting to note that the growth may appear long after tarring has been abandoned, and in rare cases it has followed, after many months, when only a single application of tar has been made. Physical injury to the tarred skin, such as may be obtained by scarification, shortens the period of induction.

However extensive the surface tarred, only a single carcinoma develops, and when this happens any neighbouring warty growths disappear. This phenomenon is sometimes seen in various forms of paraffin cancer in man, and it suggests that possibly the presence of the malignant tissue induces retrogressive changes in neighbouring simple tumours, or more active defensive processes in the surrounding connective tissues.

Many attempts have been made to isolate the actual carcinogenic substances present in coal tar, and this has recently been achieved by Kennaway, Cook, Hieger and their associates. It was found several years ago that the active substances are present in largest amount in high temperature distillates of coal tar, and later it was noted that such distillates possess a characteristic fluorescence spectrum. Synthetic substances with similar spectra were then tested by applying them to mice. Amongst the substances tested was the chemical compound 1 : 2 : 5 : 6-dibenzanthracene, which had been newly synthesized by a firm of manufacturing chemists, and this was found to be actively carcinogenic. During the last few years a number of products allied to dibenzanthracene have been obtained, both by synthesis and by extraction from coal tar (*see also* p. 73).

PRECANCEROUS STATES IN MAN

It is now recognized that in a certain proportion of cases malignant tumours in man arise upon a basis of some chronic lesion of a simple nature. From some long-continued irritative process the tissues undergo prelude changes of a proliferative nature which eventually culminate in cancer. It is hardly an exaggeration to state that study of these precancerous states constitutes one of the most fruitful avenues for cancer research and one in which there is prospect of fresh advances.

It has long been known that certain tumours arise on the basis of *congenital and inherited abnormalities*. (Malignant growths may take origin, for example, in ectopic testes, in pigmented warts, in neurofibromatosis and other congenital lesions; the intensely malignant glioma of the retina occurs as a familial disorder; whilst carcinoma of the large intestine arises not infrequently upon the basis of an inherited lesion; *polyposis coli*.)

Simple tumours occasionally become malignant, *e.g.*, fibromyoma of the uterus; though the great majority of simple tumours are no more liable than are normal tissues.

Various forms of *chronic irritation* constitute the last and in some respects the most important group of the precancerous conditions occurring in man.

Carcinoma arises as a result of innumerable forms of chronic irritation. Carcinoma of the skin commonly occurs on a basis of old ulcers, burns, lupus, and the like; carcinoma of the mouth

or the lip commonly follows leukoplakia, or hyperplasia resulting from irregular teeth or the use of a clay pipe; carcinoma of the penis occurs when there is irritation from smegma retained behind a tight foreskin—it is consequently almost unknown in Jews; carcinoma of the stomach may arise at the edge of an old ulcer; carcinoma of the gallbladder may follow gall-stones. Lastly there are the tumours known as occupational cancers, which will be described separately below.



FIG. 20. Cancer of the gall bladder, presumably associated with chronic irritation by the gall-stones. The tumour, a scirrhus carcinoma, has infiltrated the gall bladder wall and produced an hour-glass deformity.

(Department of Surgery, University of Edinburgh.)

The relationship of these forms of chronic irritation to cancer will be discussed on a later page. It is sufficient here to note their great diversity of character.

Some are physical agencies, others chemical, and others again result from infection or infestation. This diversity would, at first glance, seem to indicate that there is no specific activity involved, and it is generally believed that the irritants do not actually cause cancer, but merely prepare the tissues for its origin. It is noteworthy that malignancy rarely develops unless the irritant has been effective during a considerable time, or has been frequently repeated, and that it may develop several years after the cause of irritation has been removed. The general view is that the effect of the chronic irritation is to interfere with cell nutrition, perhaps as a result of lymph stasis, and thus to render the cells more liable to undergo malignant proliferation.

OCCUPATIONAL CANCERS

Owing principally to modern scientific and industrial developments the number of occupational cancers is now considerable, and there is little doubt that it will increase in the future. There are a few tumours in this class, however, that date from long before the industrial era. Chimney-sweeps' cancer of the scrotum, resulting from the prolonged action of coal-tar products present in soot, is one of these. Another is the khangri cancer so common in Kashmir. The khangri is an earthenware jar contained in a basket and filled with burning charcoal, which the Kashmiri carries for warmth under the clothes in close contact with the abdomen, and it frequently causes burns which heal with much cicatrization. The scars very often become the site of development of a carcinoma.

The irradiation cancer (*see* p. 105), which has taken its melancholy toll of so many of the pioneers of radiography, is a familiar example of

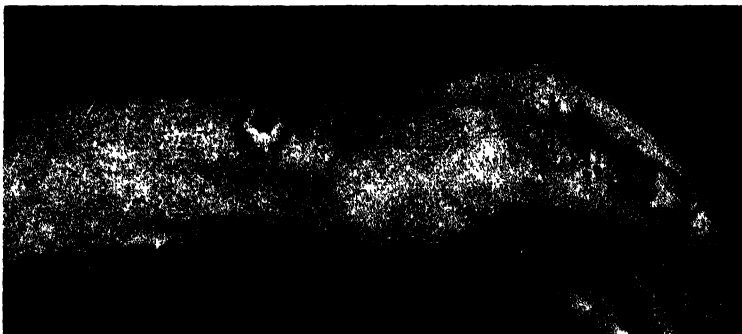


FIG. 21. Shale oil cancer. A squamous-cell carcinoma, in a man aged fifty-five years, who had worked in the paraffin refinery during twelve years. A warty dermatitis had been present for several years, and the carcinoma developed in one of the warts.

an occupational cancer, and there are too the carcinoma of paraffin refiners and mule spinners, the bladder tumours of aniline dye workers, the pulmonary tumours of certain cobalt miners, and several others less well known.

Occupational cancers vary greatly in frequency, incidence, and clinical course, but practically all have these features in common: (1) the growth arises in men exposed for a period of years to the particular carcinogenic agent; (2) in the great majority of cases the growth is preceded by some precancerous condition, such as various forms of dermatosis; (3) the growth may begin many years after the worker has changed his occupation; (4) growths occur only in a small proportion of exposed persons, depending presumably on some idiosyncrasy.

Shale Oil Cancer. This form of cancer, though rare, is of interest owing to its relation to a particular industry. The tumour is almost limited to the West Lothian district of Scotland, where it affects

those engaged in the refining of shale oil (paraffin). It is a carcinoma and occurs principally on those parts of the body exposed to prolonged contact with the oil; in half the cases it occurs on the scrotum, in 80% on the upper extremities, and in the remainder chiefly on the face. Usually the tumour appears in men who have served during ten to forty years in the refineries, and it is uncommon in those of shorter service. It often occurs many years after retirement from work.

Scott showed that in most cases it occurs in men actually engaged in the refining process, and consequently in regular contact with hot oil. The cancer develops on a papular eruption or on a wart associated with a dermatosis such as frequently affects these workers. In other cases, however, the tumour arises in labourers who are little exposed to the oil, and in them it is not preceded by an obvious dermatosis. Presumably in such cases there is an idiosyncrasy.

Mule Spinners' Cancer. This is another form of paraffin carcinoma. It occurred in the "mule" spinners of Lancashire cotton mills, and did not appear to be known in cotton-spinning districts in other countries. The "mule" required constant lubrication, and much of the oil was sprayed off the machine, especially at about the hip level. The men were thinly clad, on account of the high temperature at which mule-spinning was carried on, and their clothes became saturated with oil. The cancer affected the scrotum, neck and arms. It usually occurred in spinners of twenty to forty years' service, and was often preceded by wart formation.

It is interesting to note that mule-spinners' cancer showed a rapid increase in Lancashire during the early part of this century. This is believed to be related to the fact that the period 1850 to 1875 saw a gradual transition from the use of animal (non-carcinogenic) oils to mineral oils derived from shale or petroleum. Only after the latent period of forty to sixty years did the effect of this change become manifest—a disturbing observation when considered in regard to the possible effect, many decades hence, of the modern pervasion of other petrolates.

THE ORIGIN OF TUMOURS

No problem in the whole of pathology has evoked such a plethora of writings that "darken counsel by words without knowledge," of explanations that do not explain, and of theories that are insufficiently comprehensive. Few subjects offer greater perplexity and confusion to the inquiring student; and few are more difficult to present within unavoidably narrow limitation of space.

To understand the principal theories held in regard to the origin of tumours, and to appreciate the significance of recent experimental findings, we must consider some of the fundamental features of tumour growth. In particular we must examine the behaviour of the tumour cell and discover in what respects it differs from normal cells.

The Biology of the Tumour Cell. It is a characteristic of nearly all tumours that their cells resemble more or less closely the cells of the tissue from which they are derived, and this similarity of appearance

holds good for the primary growth and for any metastatic growths that may develop.

In spite of this morphological resemblance, it has until recently been the general opinion that tumour cells must differ from normal cells in some fundamental respect, in virtue of which they are endowed with a limitless capacity for proliferation.

Many attempts have been made to discover wherein this difference lies, and to demonstrate in tumour cells a peculiar feature either of internal structure or of metabolism. It was claimed, for example, that tumour cells differ from normal cells in the number of their chromosomes, and when this was shown to be erroneous it was suggested that they differ in the character and disposition of the chromosome-constituents, the genes.

On the chemical side, the work of Warburg has furnished many interesting observations. It has long been recognized that cells, like bacteria, may be aerobic or anaerobic. Aerobic cells require oxygen for their nutrition, and derive their energy from the combustion of carbohydrates to carbon dioxide and water; anaerobic cells can live in the absence of oxygen by the fermentation of carbohydrates to lactic acid (anaerobic glycolysis). Now Warburg has shown that whereas the great majority of normal cells require oxygen, malignant cells subsist principally by anaerobic glycolysis, even though oxygen be available. According to Warburg, this property is an essential characteristic of malignant cells, and enables them to proliferate in circumstances inhibitory to normal cell growth. Even in this respect, however, malignant cells only differ from normal cells in degree, not in kind, for it has been shown that certain normal cells, for example those of the retina, possess glycolytic faculties equal to those of malignant cells, and to a smaller extent many other normal cells are similarly endowed, especially when actively growing.

During recent years most authorities have come to believe that tumour cells do not, in fact, differ in any fundamental respect from normal cells, and that their capability for limitless growth is not due to a special biological property but rather to freedom from restraint.

Nicholson, in a series of valuable papers, has lent the full weight of his authority to the view of the fundamental similarity of normal and malignant cells. He points out that tumour cells do not differ in essentials of structure or of growth from the cells of normal tissues, and that many simple tumours approach very closely in appearance to developmental malformations. A continuous gradation may be recognized, for example, from uniovular twins at the one extreme through parasitic foetuses, teratomata and mixed tumours to the most highly malignant neoplasms. In his opinion, tumour formation is simply the expression of one of the physiological potencies of every living cell.

It is often stated that tumour cells are peculiar in their property of unlimited proliferation. It has been shown, however, by tissue culture experiments that this property is possessed also by many normal cells, provided that they are suitably nourished. Carrel, for example, has succeeded in propagating normal fibroblasts upon artificial media for

as long as twelve years, and other normal cells have been maintained in active proliferation for shorter periods.

Thus an inborn propensity for limitless growth is a characteristic feature of many, if not all cells. Normally their growth is restricted and controlled, so that the cells proliferate only to the extent necessary to meet the needs of the organism as a whole. In tumours, on the other hand, cell proliferation is unrestrained.

Older Theories upon the Origin of Tumours. Upon the observation that cancer sometimes develops at the site of congenital abnormalities, Durante advanced the view, later to be supported by Cohnheim, that tumours do not arise in normally placed tissues but in aberrant "cell rests." It was postulated that in the course of foetal life certain groups of cells failed to develop normally but persisted as "rests," which either remained embedded in their proper environment or were misplaced in other parts of the body, and it was believed that these "rests" retained special powers of growth which enabled them, after long periods of latency, to proliferate and form tumours. It is well known that portions of the adrenal and parathyroid glands and of the pancreas were often so displaced, and it was supposed that similar malformations occurred in relation to other organs and other tissues.

Ribbert accepted the general principles of Cohnheim's theory, but extended it to include also acquired epithelial displacements, such as may occur from overgrowth and fibrosis around any chronic inflammatory process. In Ribbert's view, islets of epithelial cells cut off from their normal relationships became released from physiological control and thus attained autonomy.

These and collateral theories held the field for a long time, but it is now recognized that they fail to explain many of the known facts of cancer and are totally inadequate except perhaps for a small proportion of tumours. For cancer cannot arise in "cell rests," unless these be ubiquitous; Ribbert's theory cannot be applied to sarcoma. Moreover, it is very doubtful if such "rests" as are known to occur are any more liable to neoplastic change than normal tissues. The time-honoured example is the development of hypernephroma in adrenal rests in the kidney, but even this is now unacceptable, for most histologists believe the hypernephroma is of renal, not adrenal, derivation.

The Parasitic Theory of Cancer. Many attempts have been made to demonstrate an organism as the cause of cancer, and there are few types of organism that have not from time to time been incriminated, but, with the exception of Fibiger's nematode and one or two other parasites known to be related to specific forms of tumours, none has stood the test of confirmatory experiment and none has received general acceptance. Many alleged parasites are now regarded as cell inclusions of various sorts, and others are generally looked upon as contaminants.

The parasitic theory has obvious attractions, but there are almost insurmountable obstacles to its acceptance, and all experienced pathologists are agreed that it is not consistent with the known facts. The greatest difficulty is to account for the narrow species limitation and at the same time the wide zoological distribution of cancer. If cancer is

caused by a single universal parasite, why cannot the disease be propagated from one species to another?

To overcome this difficulty Gye has recently formulated an ingenious hypothesis, which invoked a second, specific factor as well as a universal parasite. Gye's work was carried out principally upon the Rous chicken tumour, a peculiar form of sarcoma which differs from all mammalian growths in being propagable from chick to chick by means of filtered, cell-free extracts. By centrifuge and by other methods Gye was able to separate such extracts into two moieties, which were innocuous alone but potent when mixed. These portions he believed to contain respectively the parasite and the second factor. As a result of these and other experiments Gye came to the conclusion that the parasite is present in all tumours, and is of the nature of an ultra-microscopic, filter-passing virus. The second factor, which is thermo-labile and usually known as the "chemical factor," is specific for each species and for each type of tumour.

Ingenious though the hypothesis is, it has not proved acceptable, and his experimental results at present lack confirmation.

Recent Work on Carcinogenic Agents. During recent years, the most notable progress in cancer research has been upon the relationship of cancer to various forms of so-called chronic irritation, and particularly upon the characteristics of various agents capable of producing cancer experimentally.

In a previous section (p. 67) attention has been directed to the number and variety of the diseases that may be regarded as pre-cancerous. It has been shown that cancer occurs as a sequel to many chronic inflammatory processes (burns, ulcers, lupus, cholecystitis, etc.) or as a result of such diverse agencies as X-rays, soot, various paraffin products, arsenates and aniline dyes. It has, moreover, been related how cancer can be produced experimentally in animals by certain parasites or by coal-tar products and other chemical substances. Thus it is apparent that the precancerous lesions are of widely differing character, some physical in nature, others chemical, and others again resulting from chronic infection or infestation. In view of their diversity of character, it is difficult to suppose that these agencies initiate the process of cancer in virtue of any single common factor, and most authorities hold the view that they do not actually cause the malignant change but rather prepare the tissues for its development.

Experimental investigation of the carcinogenic constituents of coal tar has recently yielded information that may well prove to be of the utmost importance in regard to the origin of tumours. Ever since the early experiments of Yamagiwa and Ichikawa (*see* p. 66), attempts have been made to isolate the active substances present in the tar, and this has at last been achieved by Kennaway and his associates at the Cancer Hospital, London. The active substances have not only been isolated in a pure state, but have been prepared synthetically.

When the coal-tar products were first investigated it was found that the carcinogenic activity was greatest in high temperature distillates of the tar. Later it was found that these active distillates differ from the inactive fractions in possessing a characteristic fluorescence spectrum,

whose intensity varies more or less in proportion to the potency of the preparation. Attention was then directed to synthetic chemical substances known to exhibit a similar spectrum, and some of these also proved to have cancer-producing properties.

The most remarkable feature is that these substances are all closely similar in chemical composition. They are hydrocarbons, and each has a molecule containing four or five carbon rings arranged in a condensed formation. The majority are related to 1:2-benzanthracene, a substance which itself has hardly any cancer-producing activity. The most potent of them yet discovered are 1:2:5:6-benzanthracene and 1:2-benzpyrene.

Thus in this particular series of cancer-producing agents, carcinogenesis appears to be linked up with a special type of molecular structure. It is interesting to note that a somewhat similar structure is found in several substances normally present in the body, for example, œstrin and sterols such as cholesterol and the bile salts, and possibly the male hormone and vitamin D. It has been suggested that these substances may, under the influence of chronic inflammatory processes, X-rays or other agencies, undergo alterations of molecular structure and assume carcinogenic properties.

The conversion of one of these normal body fluids into a carcinogenic substance has already been achieved. By *in vitro* experiments the bile acid deoxycholic acid has been converted into the intermediate product dehydronorcholene and then by dehydrogenation into methylcholanthrene, which is actively carcinogenic when applied to the skin of mice. On general chemical grounds, however, it is doubtful if such a process can take place within the human body.

From the foregoing, it will be seen that our knowledge of the agents responsible for tar cancer has extended rapidly within recent years. It would clearly be dangerous to apply the findings in one particular type of cancer to the origin of malignant disease as a whole, but, nevertheless, the success gained in this limited field warrants the belief that in time the solution of the greater problem will in turn be achieved.

CLASSIFICATION OF TUMOURS

In the present state of our knowledge no classification of tumours is beyond criticism, nor is any likely to be so until the ætiology of tumour formation is more clearly understood.

Tumours may be classified in either of two principal ways: (1) on a histological basis, according to the type of cell or tissue of which the tumour is composed, and (2) on a histogenetic basis, according to the primitive cell layer from which the tissue is thought to be derived.

There are so many intermediate and mixed types of tumour, and so many tumours of unknown or disputed origin, that any classification has patent disadvantages. For the sake of simplicity the following arrangement will be adopted here:—

(1) Non-malignant Tumours of Connective Tissue Origin.*Fibroma.**Xanthoma.**Lipoma.**Myxoma.**Chondroma.**Osteoma.**Myoma.**Glomangioma.***(2) Malignant Tumours of Connective Tissue Origin.***Sarcoma.***(3) Non-malignant Epithelial Tumours.***Papilloma.**Adenoma.***(4) Malignant Epithelial Tumours.***Carcinoma.***(5) Teratoma and other Mixed Tumours.****(6) Tumours Derived from Nerve Tissue.***Glioma.**Neurinoma.**Ganglioneuroma.**Paraganglioma.**Glomangioma.**Argentaffinoma.***(7) Tumours Derived from Endothelium.***Endothelioma.**Hæmangioma.**Lymphangioma***(8) Melanoma.****(9) Chorion Epithelioma.**

In addition to these, there are a number of rare, obscure or indeterminate tumours which in the light of our present knowledge defy accurate classification. Such tumours as the giant-cell tumour of bone, chordoma, and odontoma belong to this group.

FIBROMA

Simple fibrous-tissue tumours are widely distributed and are very common. Many of them, although termed fibroma, are actually of a more complex nature. A fibroma in the breast, for example, generally contains glandular acini, and in the present state of our knowledge is more accurately termed fibro-adenoma.

A fibroma may arise from any of the fibrous connective tissues of the body, such as fascial planes, intermuscular septa, and submucous layers, or from the connective tissue stroma of such organs as the breast, kidney, and ovary.

The common tumours arising from nerve sheaths were formerly regarded as fibromata. They are now believed to be of nervous origin and are classified as neurinoma (p. 318).

A fibroma varies somewhat in structure and appearance, according

to its cellularity and rate of growth, and it is customary to recognize two principal forms, hard fibroma and soft fibroma. These do not represent distinct types, however, and intermediate varieties may occur. A *hard fibroma* is usually small and of slow growth. It is of tough consistency, and when cut across it imparts a creaking sensation like cartilage. The cut surface is of grey colour and is traversed by glistening bands of fibres. Microscopically, such a tumour is composed of fibrous tissue of adult type, irregularly arranged in broad columns which pass in all directions. Cells are comparatively scanty, and there is a considerable proportion of collagen, often in a state of hyaline degeneration. Sometimes the cells have a somewhat whorled arrangement. A *soft fibroma* tends to grow more rapidly and to attain somewhat larger size. Microscopically, it is more cellular and with scanty fibrillar material. Some soft fibromata are so cellular as to resemble sarcoma. A *recurring fibroma* takes an intermediate position between a simple growth and a sarcoma. At first it is of a simple type and grows slowly, but after operation recurs repeatedly as if locally malignant and eventually may assume sarcomatous characters. The "desmoid tumour" of the abdominal wall, the "recurring fibroid of Paget," is of this type (see p. 221).

Keloid. Under the title of *true keloid* (as distinct from the common keloid of Alibert), Addison described a rare disease of the skin and subcutaneous areolar tissues. This remarkable disease arises spontaneously and is indicated first by a small oval white opacity or morphea in the skin. A zone of redness surrounds the patch, which later exhibits yellow or brown mottling. Following the development of new fibrous tissue, the surrounding skin becomes hard and rigid and processes of scar tissue extend for a considerable distance in the subcutaneous tissue. Finally the affected part, frequently an extremity, becomes hide-bound and the seat of contractures. The skin, which may be excoriated, is puckered and nodular with a yellowish pink colour, giving it a resemblance to an extensive imperfectly cicatrised burn. The disease is progressive during many years and may implicate large areas of the body and limbs, and be associated with great pain and irritation. This variety of keloid is probably identical with scleroderma.

The surgeon is more familiar with keloid as a condition of excessive overgrowth of a scar, which results in firm, irregular, claw-like masses of fibrous tissue projecting above the surrounding skin. The lesions may be single or multiple. The common places of origin are the face, neck and ears, and the front of the thorax and abdomen.

The lesion may follow any kind of injury, and it occurs in the scars of burns, tuberculous sinuses, vaccination marks, and healed skin diseases, as well as in those of surgical wounds. Even insignificant injuries such as insect bites and pin pricks have been the starting point of the disease.

A decided predisposition to overgrowth of scar tissue and keloid exists in some subjects. Negroes exhibit this tendency more obviously than whites, and it is stated to be pronounced in tuberculous subjects. Infection of the original wound is undoubtedly a common predisposing factor, and it is the only known one of any significance.

A recently developed keloid has the appearances of a redundant scar and has a shiny pink or reddish appearance. Its surface may be smooth, rough or furrowed, and in some sites, such as the lobe of the ear, it may be pendulous. The margins of a keloid are not sharply defined and project irregularly into the subcutaneous tissues or even into the deep fascia and muscles.

Histologically, a keloid has the structure of a soft fibroma, and is composed of dense bundles of fibrous and hyaline connective tissue with well-defined fibroblasts, which are disposed more or less parallel to the cutaneous surface. The periphery is more cellular than the centre and shows a round-cell infiltration. There are no hair follicles, sweat glands, muscle fibres, or elastic tissue in the tumour, but newly formed blood and lymph vessels are present. The overlying epidermis is thin and is often devoid of papillæ.

A keloid shows no tendency to disappear spontaneously; and it tends to recur, especially if removed during its active period of growth. Although it exhibits some of the characters of a malignant growth it never gives rise to metastases.

XANTHOMA (*Xanthelasma*)

The term xanthoma is applied to a group of yellowish-brown growths of the skin which present very diverse characters. The tumours are situated most commonly in the eyelids (*Xanthoma palpebrarum*), where they may be single or multiple. Less often they have a diffuse distribution throughout the cutaneous surfaces (*Xanthoma multiplex*). Rarely they have been observed in the pharynx, in the mediastinum, and in serous membranes such as tendon sheaths. Xanthoma sometimes occurs in association with diabetes (*Xanthoma diabeticorum*).

Histologically a xanthoma shows the characteristics of a benign connective tissue tumour localized to the corium. It is distinguished by the presence of numerous large rounded mononuclear cells, containing droplets of cholesterol esters and of orange-yellow lipid material. In ordinary fixing agents these droplets are dissolved, and therefore leave vacuoles in the cytoplasm, hence the name "foam cells."

The origin of the characteristic "foam cells" is uncertain. Some trace them to fixed cells of the connective tissue or to the endothelium of lymph or blood vessels, others to wandering phagocytic cells. Ewing



FIG. 22. Subcutaneous xanthoma. $\times 120$. There are numerous large "foamy" lipid-containing cells in the dermis and subcutaneous tissue.

(Royal College of Physicians of Edinburgh.)

believes that many xanthomatous tumours of the skin are due to lipoid infiltration of cutaneous neurofibromas.

Xanthoma palpebrarum may affect either the upper or the lower eyelid and is often bilateral. The tumours, which are of slow growth, are usually flat and bean-shaped and have a canary yellow or muddy brown colour. They are soft and are situated in the subepidermal layer of the skin.

Xanthoma multiplex occurs particularly in young subjects and is sometimes congenital. The lesions, which resemble pigmented fibrous tumours, are specially common in the neighbourhood of joints as well as on the face and trunk. They may be arranged in groups with a symmetrical distribution.

A number of the subjects of this form of xanthoma subsequently develop diabetes, and in many of the recorded cases jaundice has been present.

Probably the most common predisposing cause of xanthomatous tumours is hypercholesterolaemia, which has been shown to be present in some cases. This view is supported by the observation that the intracellular lipoid is a compound ester of cholesterol and fat, such as is normally present in such organs as the ovary and suprarenal gland, and, in certain conditions of disease, in the gall bladder, spleen and blood vessels. Such a metabolic predisposition would explain the occurrence of xanthoma in diabetes and in jaundice, states often characterized by an increase of the cholesterol content of the blood.

It is interesting to note that xanthomatous tumours may be produced experimentally in rabbits fed with large amounts of cholesterol and subsequently submitted to aseptic traumatization of the subcutaneous tissues. The cholesterol is deposited from the blood and subsequently undergoes phagocytosis by large mononuclear cells, and these cells assume the characteristic "foamy" appearance.

Under the general heading Xanthomatosis we may include certain other diseases characterized by the accumulation of lipoid-laden cells in various organs or tissues. Amongst these are *Gaucher's disease*, a chronic familial affection occurring in children, especially females, and characterized by great enlargement of the spleen due to the accumulation of cerebroside within its reticulo-endothelial cells; the *Niemann-Pick disease*, a rapidly fatal disease of Jewish infants, characterized by enlargement of the spleen and liver due to the accumulation of phosphatids such as lecithin; and the *Schüller-Christian disease*, in which xanthomatous tumours occur in the bones, especially of the skull.

LIPOMA

A lipoma is the commonest tumour of the subcutaneous tissue and may occur in almost any part of the body, although it shows a predilection for the regions of the shoulder, back, and buttocks. Less commonly a lipoma grows in an intermuscular space, under the periosteum, or in the submucous or subserous layers of the alimentary canal. It is a soft, well demarcated, movable swelling which is very often lobulated. The overlying skin is often loosely attached at one or more points to

the capsule of the tumour and is therefore obviously dimpled, or becomes so on pressure.

A lipoma appears in adult life and usually grows very slowly, and having attained a certain size remains stationary, but occasionally growth is rapid and the tumour may attain a very large size. When situated in the back it may, by gravity, gradually alter its position. In the region of the buttocks, the groin, and the perineum it often becomes pedunculated.

A lipoma is usually composed of round fairly firm, yellow masses or lobules. It is surrounded by a fibrous capsule which is firmly connected with the surrounding tissues, but only loosely connected with the tumour. Protrusions of the capsule pass between the lobules of the tumour and constitute its fibrous trabeculae.

A lipoma is essentially a benign tumour, and sarcomatous change

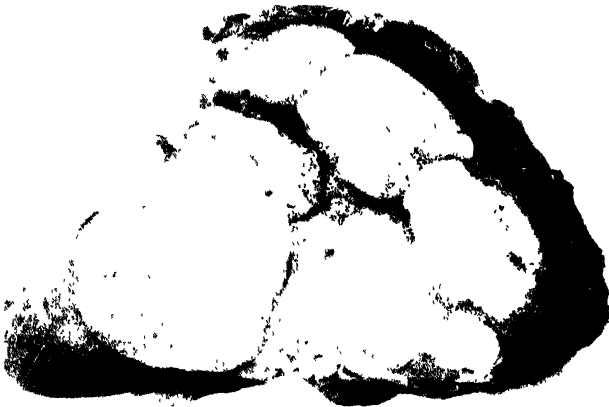


FIG. 23. Lipoma removed from the thigh of a man aged sixty-three years. The lobulated character of the tumour is clearly seen.

(By courtesy of Mr. J. W. Struthers.)

is exceedingly rare, although primary tumours of the nature of *liposarcoma* have been described. They occur mainly in the retroperitoneal tissues or subcutaneously in the shoulder region. They invade diffusely, and may be painful. In most cases they are of low malignancy and responsive to irradiation therapy.

Some lipomata have an abundant and dense fibrous stroma and may be appropriately called *fibro-lipoma*; others are excessively vascular—*haemangio-lipoma*; and others again present myxomatous, cartilaginous, and xanthomatous elements. Occasionally a lipoma of long duration undergoes degenerative changes such as liquefaction and calcification.

Multiple lipomata are not uncommon. The individual tumours in this condition are seldom large, but they may be very numerous and scattered over the whole of the body surface, and as many as 2,000 have been present in one subject. In some instances they may be

symmetrically disposed, as in the forearm, where they are sometimes painful and associated with motor, sensory and trophic disturbances.

A *diffuse lipoma* (pseudo-lipoma) usually occurs in the subcutaneous tissues and intermuscular tissues of the neck of men, where it gives rise to a bulky collar-like swelling. It is not a true tumour but a localized overgrowth of the fat of this region, which in some cases can be attributed to chronic alcoholism. Somewhat similar overgrowths may occur in the hips and thighs, especially in women. From their tendency to give rise to severe pain these overgrowths have been given the name *adiposis dolorosa*.

Excessive deposits of fat may occur in the supraclavicular region in myxœdema, and in the genital area in hypopituitarism.

MYXOMA

A myxoma is a soft tumour composed of translucent jelly-like tissue resembling the delicate mesenchyme of the umbilical cord (Wharton's jelly). Microscopically, it consists of branching stellate cells set in a clear mucoid matrix. Such tumours arise usually in relation to tendons, periosteum or joints, or occasionally in the heart. They are usually small, encapsuled growths, but sometimes attain large size. A pure myxoma is an extremely rare growth, but tissue of the character just described is of frequent occurrence in other tumours, such as nasal polypi, a chondroma or sarcoma. In such circumstances it is to be regarded as resulting from degenerative changes (mucoid or myxomatous degeneration).

CHONDROMA AND OSTEOMA

These tumours are considered fully in the chapter on "Diseases of Bones," to which reference may be made (*see p. 158*).

MYOMA

Muscle tumours may be composed of either plain or striped muscle fibres. A *leiomyoma*, or tumour of plain muscle fibres, is by far the commonest. The site most frequently affected is the uterus, and the uterine myoma is one of the commonest of tumours in the whole body (*see p. 684*). Less often a leiomyoma arises from the muscle fibres of the œsophagus, the stomach (*see p. 474*), the bladder, or ovary. Rare examples have been found in the skin, and are believed to arise from the *mm. arrectores pilorum*. A leiomyoma is usually a benign encapsuled growth, but occasionally it is subject to sarcomatous change. It is described fully on p. 684.

A *rhabdomyoma* is a tumour composed of well differentiated striated muscle fibres. It is exceedingly rare but has been encountered most often in young subjects especially in the soft palate and the tongue, and less often in the bladder, the uterus, the vagina, and the œsophagus. When the tumour arises from a mucous surface its appearance is characteristic, showing a lobulated coarsely polypoid structure with broad clubbed processes. It is locally destructive and may metastasize

by the lymph channel or be disseminated in the blood stream. In structure a rhabdomyoma appears superficially to be well differentiated, but a closer examination reveals groups of very anaplastic or primitive round and spindle cells to which it probably owes its very malignant tendencies.

Some examples of rhabdomyoma are composed entirely of undifferentiated cells resembling morphologically and in staining characters primitive muscle cells—*myoblasts*. Such tumours have a homogeneous cellular pattern, and though the cells lack the mature cellular structure of a typical rhabdomyoma, the tendency to malignancy is much less. This type of rhabdomyoma has been styled *myoblastoma* by Cappell and Montgomery.

Striated muscle of varying degree of maturity is an occasional constituent of teratoid tumours, *e.g.*, of the kidney, testis, and ovary.

SARCOMA

Malignant tumours derived from connective tissues are generally of extreme malignancy. They grow rapidly, invade surrounding tissues, disseminate to distant parts of the body at an early stage, and quickly lead to a fatal issue. Within the bounds of this general statement there are, however, many variations in behaviour. Some sarcomata, notably those arising in bone, are almost invariably fatal, but others are less aggressive, while a few only achieve recognizably malignant characters after a prolonged existence.

A sarcoma is much less common than a carcinoma, and differs from it in several important attributes. Sarcoma may occur at any age, though some forms, notably bone sarcoma, are most common in early life. A sarcoma generally grows rapidly and forms a large soft tumour. With few exceptions it tends to disseminate early by the blood stream. This method of dissemination is no doubt chiefly due to the copious blood supply of a sarcoma and to the delicate nature of their vessel walls, which are readily invaded by tumour cells.

A sarcoma may arise from any type of connective tissue, and it consequently has a wide distribution in the body. They originate most often in relation to bone, or from the periosteum, cartilage, fascia, and intermuscular septa or in the subcutaneous tissues; less often they occur in submucous tissues or in the stroma of internal organs.

In a certain proportion of cases a sarcoma arises in a previously benign tumour, *e.g.*, uterine myoma, fibroma, chondroma. Sometimes it arises on a basis of some generalized growth disorder, *e.g.*, neurofibromatosis, osteitis deformans, osteitis fibrosa. Occasionally trauma appears to determine the onset of the growth.

The cells of a sarcoma may remain fairly well differentiated and continue to reproduce, to some extent, the structure of the parent tissue, or they may revert completely to the primitive state. Thus a sarcoma arising in fibrous tissue may continue to produce more or less well-formed collagen fibrils or may be entirely cellular. When the nature of the parent tissue is recognizable, such terms as fibro-sarcoma,

chondro-sarcoma, osteo-sarcoma, lipo-sarcoma, and myo-sarcoma may be employed. Tumours composed of undifferentiated cells are usually described according to the predominating type of cell, *e.g.*, round-cell, spindle-cell, mixed-cell.

Naked Eye Appearance. There are so many forms of sarcoma that no general statement can replace the detailed description of individual types. In general, however, it may be said that most sarcomata form bulky, soft tumours of fleshy appearance and great vascularity. Others, such as fibro-sarcoma, however, are firm and relatively pale, and sarcoma arising in bone may be calcified, even to ivory hardness. They are not encapsuled, and invade surrounding tissues freely, although they may be limited temporarily by such structures as periosteum

or cartilage. Since the blood vessels of a sarcoma have thin walls and are ill-supported, there is a great tendency to hæmorrhage. Mucoid change and other forms of degeneration and necrosis are usual, and lead to liquefaction and to the formation of spurious cysts.

Microscopic Appearance. A sarcoma is composed of cells of the connective tissue type embedded in various amounts of intercellular matrix. Spindle-shaped and round cells may be present, and in rapidly growing tumours giant cells may develop as a result of irregular nuclear division. The outlines of



FIG. 24. A mixed-cell sarcoma of bone. $\times 275$. The tumour is highly cellular and pleomorphic. It contains spindle cells, round cells, and giant cells of various size. Note the nuclear hyperchromatosis. The capillary vessels of the tumour were thin-walled and many of them were supported only by tumour cells.

(Laboratory of Royal College of Physicians of Edinburgh)

sarcoma cells are usually indistinct, but the nuclei, on the other hand, are clearly defined, and are usually large, hyperchromatic and vesicular. Mitotic figures are usually present, and may show various irregularities of form. A striking feature of most sarcomata is the character of the blood vessels, which are large and very thin-walled. Often they are lined only by endothelium, and even this coat may be lacking in places, so that the blood flows through irregular clefts in close contact with malignant cells.

In most sarcomata the predominating cells are spindle-shaped (*spindle-cell sarcoma*). The cells may be large or small, and in their general characters they resemble young fibroblasts. Sometimes the tumour is comprised almost entirely of such cells, and intercellular

substance is lacking. Such cellular tumours are usually very malignant. In other examples the intercellular substance is more abundant and contains collagen fibrils (*fibrosarcoma*). Occasionally a sarcoma is composed of such well-differentiated cells and matrix that the distinction from a simple fibroma, or even from granulation tissue, may be made only with great difficulty.

Other sarcomata are composed principally of small round cells. Most of these are *lymphosarcomata*, tumours which arise in lymphoid tissue, and differ in many respects from other sarcomata (*see* p. 257). Other sarcomata are described, but recent researches show that they are extremely rare, and that most tumours formerly so classified are lymphosarcomata.

Many other varieties of sarcoma are recognized, according to special features of the cells or of the intercellular matrix—for example, chondrosarcoma, osteo-sarcoma, myxo-sarcoma, and lipo-sarcoma. These are described on other pages.

PAPILLOMA

A papilloma is a simple epithelial tumour which projects from an epithelial surface. Although essentially an epithelial structure, it always includes connective tissue elements, which form a core, simple or branching, containing lymph and blood vessels. It appears as though

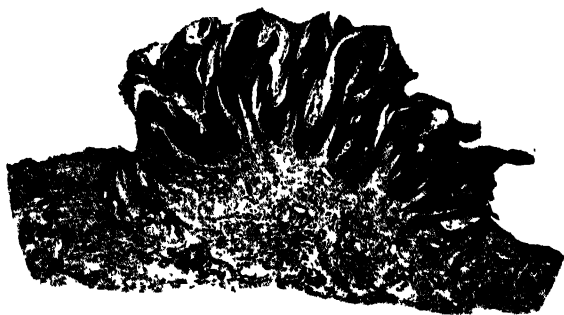


FIG. 25. Papilloma of the skin.

(Laboratory of Royal College of Physicians of Edinburgh.)

the growing epithelium can demand a connective tissue framework to support and nourish it.

A papilloma may arise from any epithelial surface, and the following types may be recognized: (1) from the epidermis, (2) from mucous membranes, (3) from duct walls, (4) in certain cysts and cystic tumours.

Cutaneous papillomata are common in childhood, and are usually multiple, the skin of the hands and fingers being frequently affected. The growths are the result of a virus infection, and after a varying period tend to disappear spontaneously. Venereal papillomata, which affect the skin of the genital organs, are also of infective nature. As Cathcart suggested in 1897, they are not due to gonococci, and there is evidence to suggest that they arise from some form of filter-passing organism.

A papilloma arising from epidermis or from any squamous cell membrane, such as the mucous membranes of the tongue, mouth, larynx, œsophagus or vagina, is composed of a core of connective tissue surmounted by squamous epithelium. The epithelium may resemble the normal tissue, but often presents variations, such as undue thickening of the rete Malpighii or of the stratum corneum.

Villous papilloma of the bladder and renal pelvis forms a special type of tumour. It reproduces the transitional epithelium of the urinary passages, and consists of connective tissue cores surmounted by a few layers of rounded or oval cells. It is composed of innumerable filamentous processes of great delicacy, and, since the stroma is vascular, it is very apt to cause profuse hæmaturia. It frequently recurs after operation, and may eventually prove malignant (*see also* p. 649).

A papilloma is common in the large intestine, and may occur in the stomach, small intestine or gall-bladder. It is composed of columnar cells on connective tissue cores, and it is usually pedunculated. Since the columnar cells tend to reproduce to some extent the glandular structure of the alimentary tract, the papilloma is somewhat complex, and often is of the nature of pedunculated adenoma rather than a papilloma. In the colon these growths are apt to become malignant. It is interesting to note that in Egypt schistosomiasis frequently gives rise to multiple outgrowths in the bladder and rectum indistinguishable from true papillomata and equally liable to malignant change.

Papillomata arising from the ducts of glands occur with great frequency in the breast, in association with so-called chronic mastitis. They are described in more detail in the chapter on diseases of the breast. Similar papillomata are very common in the biliary tract of rabbits, where they form multiple columnar-cell outgrowths from the walls of the intrahepatic bile ducts. The peculiar interest of this condition lies in the fact that it occurs only in rabbits affected by coccidiosis, and that the oöcysts of the parasite may be seen closely related to the tumours—a striking example of new growths due to parasites.

Papillomata arising in cyst walls are seen most frequently in cysts in the breast and ovary, but may occur in other regions. The cysts referred to are not simple distension cysts, but depend primarily upon proliferation of their epithelial lining cells, and it is consequently not surprising that in some cases the proliferation takes the form of intracystic projections in place of simple enlargement of the cyst. In some cases the presence of intracystic papillomata is an indication of early or potential malignancy—the papillomata are the first evidence of the ability of the cells to grow atypically. Thus in the ovary a papilliferous cyst is considerably more liable to malignancy than a multilocular cyst.

✓ ADENOMA

An adenoma is a simple tumour derived from glandular epithelium. Like a papilloma, it also contains connective tissue which serves to support and nourish the epithelial elements. The connective tissue

varies greatly in amount and character. It may be delicate and more vascular or fibrous and less vascular. When the stroma preponderates, as in many breast tumours, the term *fibro-adenoma* may be used.

An adenoma tends to reproduce with some degree of exactness the glandular structure of the parent tissue, and indeed some adenomata, *e.g.*, in the breast or thyroid, can be distinguished only with difficulty from the normal glands. Moreover, the cells of the tumour may function; adenoma of the thyroid gland contains colloid material and may produce thyroxin; adenoma in the gastro-intestinal tract secretes mucus. Since the tumours possess no properly formed ducts, the secretion may remain impounded in the acini and form cysts, *e.g.*, in the breast, thyroid, and ovary. The epithelial wall of such a cyst may continue to proliferate and may give rise to intracystic projections of the character of papillomata. These are particularly common in ovarian cystic adenomata. An adenoma lying close to a free surface tends to project therefrom, and may eventually become pedunculated. This is very apt to occur in the gastro-intestinal tract, and the pedunculated tumour may subsequently initiate intussusception.

Adenomata do not appear to bear the same relation to chronic irritation as do papillomata, but, on the other hand, in a number of cases seem to be associated with some developmental disturbance, when they possibly originate in glandular cells dislocated from their normal environment. Foetal adenoma of the thyroid gland appears to arise in this way, as do adenomata of the colon, which, furthermore, have a familial incidence.

An adenoma may arise from any glandular tissue in the body. It occurs most often in the breast, ovary, thyroid, and glands of the alimentary tract. More detailed description of individual types is found in the chapters devoted to these regions.

CARCINOMA

This is the commonest form of malignant new growth, and is the form usually indicated by the term "cancer." Its frequency may be judged from the fact that more than 10% of those who reach the age of thirty-five years eventually die of cancer.

Carcinoma differs from sarcoma in several respects, which have already been alluded to: (1) it occurs generally later in life. The incidence rises steeply in the fifth and sixth decades, and most cases occur at this time of life. Often the age incidence of cancer coincides with the period of functional senescence of the affected tissue, *e.g.*, the breast, uterus, prostate. (2) Carcinoma usually grows less rapidly than sarcoma, and does not disseminate at such an early stage. There are exceptions to this general rule, however, notably the case of melanotic carcinoma, which often grows rapidly and disseminates early. (3) Carcinoma tends to spread first and principally by the lymph vascular system and only later invades the blood stream. (4) Microscopically a carcinoma is composed of cells of epithelial type, which tend to be grouped together in masses or columns. The individual cells lie closely

apposed to each other, with no intercellular matrix. Occasionally, however, carcinoma cells growing rapidly become spindle-shaped like the cells of a sarcoma and may lie singly in the stroma.

The amount and character of the stroma varies greatly in different tumours and in different parts of the same tumour. When in large amount and composed of tough fibrous tissue it gives the tumour a hard (scirrhus) character, and since the fibrous tissue shrinks the tumour is usually of small size. Scirrhus tumours are common in the breast, stomach and colon. In the alimentary canal the fibrous contraction may give rise to a ring stricture.

Occasionally, as in the "leather-bottle stomach," excessive stroma appears to strangle the epithelial cells, which are then identified with difficulty. Apart from such rare instances, however, scirrhus tumours are no less malignant than other types, and often tend to infiltrate widely.

A carcinoma with scanty stroma is commonly larger and softer than scirrhus growths, and sometimes it merits such a title as encephaloid or medullary. Often a tumour is scirrhus in some parts and encephaloid in others. The metastases from a scirrhus tumour

are often of encephaloid type.

Three principal types of carcinoma may be recognized: (1) squamous-cell carcinoma; (2) basal-cell carcinoma; (3) glandular carcinoma.

(1) **Squamous-cell Carcinoma** (*squamous epithelioma*). Tumours of this class may arise from the skin and its appendages or from the stratified squamous membranes of the upper air and food passages and the vagina. They may also arise by a process of metaplasia from other epithelia, e.g., from the transitional



FIG. 26. Squamous-cell carcinoma (epithelioma) of the skin. On the right there are numerous rounded masses of malignant cells, some with cell nests. Note the hyperplasia of the epidermis close to the tumour.

(Department of Surgery, University of Edinburgh.)

epithelium of the urinary tract and the columnar-cell membranes of the gall bladder, uterine neck, etc.

Squamous-cell cancer may develop spontaneously in previously normal skin, but it is particularly liable to occur at parts that have, during a long period, been subjected to some form of irritation. The

irritation may have been mechanical, thermal, chemical, or bacterial, or have resulted from various combinations of these agencies. It is therefore common for cancer to follow eczema, warts, or hyperkeratosis of the skin, and in such cases the site and character of the skin lesions, and the cancer that follows them, are usually determined by occupations that involve exposure to chemical or other irritants. Thus, in irradiation cancer, the backs of the fingers, from neglect of protection, are usually affected; in tar and pitch workers, chimney sweeps, and mule spinners the scrotum is affected. In addition to the above predisposing or precancerous factors may be mentioned chronic ulcers, cutaneous horns, the scars of burns and of lupus, and psoriasis patches. In lupus carcinoma exposure to X-rays often appears to have been the determining factor, and in psoriasis a prolonged application of arsenic often seems to be responsible.

There are two clinical types of squamous-cell cancer: (1) the papillary, and (2) the ulcerating.

The papillary type takes the form of a wart or nodule of variable size with a broad base. Ulceration tends to occur at the surface of the growth, and as a result dry crusts are formed on it. Beneath the crusts the tumour is pink in appearance, and is indurated.

The ulcerating type causes an irregular breach of the surface of the skin. The edge of the ulcer is firm and indurated, and its base is hard and granular. There may be considerable penetration into the subcutaneous tissues. On the face the ulcer may originate in a small red pimple, which grows rapidly and breaks down to form a slightly raised crateriform ulcer.

Microscopically, a squamous-cell carcinoma is composed of masses of angular cells in solid clumps with bud-like processes extending irregularly into the subcutaneous tissues, or the cells may be arranged in whorls in which the characteristic cells surround cornified epithelium (*epithelial pearls or cell nests*). The latter appearance indicates a high degree of cellular differentiation, and consequently a relatively low grade of malignancy. In some growths fibrils or spinous processes connect the cells; hence the name *acanthoma* or *prickle-cell tumour*.

A squamous-cell cancer of the skin spreads by direct infiltration of adjacent tissues. The rate of growth varies in different cases and according to the age of the subject, and the character of the tissues which surround it. Generally, warty growths tend to be less aggressive than ulcerous growths.

After a variable period the growth tends to metastasize to the regional lymph glands, which become enlarged. Visceral metastases are uncommon.

At some sites, especially the nasopharynx and tonsil, squamous-cell carcinoma may show marked anaplasia. The stroma is composed of cells of sarcomatous character (usually lymphosarcoma), so that the tumour has blended the features of carcinoma and sarcoma—*carcinosarcoma* or *lympho-epithelioma*.

Squamous-cell Cancers at Special Sites. *Cancer of the penis* starts on or just behind the glans, less often on the inner aspect of the prepuce, and very rarely in the skin of the body of the penis. In many

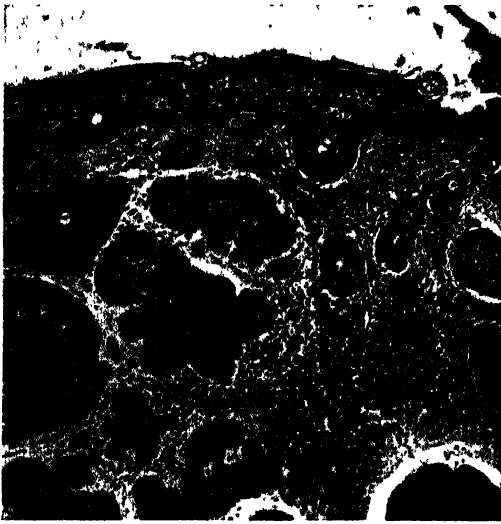


FIG. 27. Basal-cell carcinoma (rodent ulcer) of the skin. $\times 75$. The tumour is composed of large circumscribed masses of epithelial cells, the outer layers of which are of typical basal-cell character. The tumour is covered by a thin layer of skin.

instances the growth begins in a wart, an old scar, or a patch of leucoplakia. Phimosis and chronic balanitis frequently precede the development of cancer at this site, and must be regarded as predisposing factors, because the occurrence of cancer is extremely rare in the circumcised. Occasionally a glandular type of cancer occurs and probably originates in the glands at the corona or frenum.

The growth is usually of a flat papillary or cauliflower type and may reach considerable size before

ulceration occurs. The growth is pinkish-red in colour and it is firm and hard. At first it remains confined to the glans penis, but later it perforates the fibrous envelope of the corpora cavernosa and infiltrates the erectile tissue. The urethra is seldom invaded. Metastases occur in the inguinal lymph glands on one or both sides.

A carcinoma of the penis is usually concealed behind a tight prepuce; therefore its presence may only be suggested by the club-like enlargement of the organ, or by the offensive discharge or bleeding to which it gives rise.

Lupus cancer may develop at the margin of the ulcers of lupus, or in the thin scars which follow healing. Many years may elapse after healing before the appearance of the growth.

A lupus carcinoma is usually of an exuberant or cauliflower type and grows slowly, and like other cancers which develop in scar tissue it has little tendency to spread to the lymph glands, as the intervening channels are obliterated by fibrosis. In advanced



FIG. 28. Basal-cell carcinoma (rodent ulcer) in a man aged eighty-two years.

(Museum of Royal College of Surgeons, Edinburgh.)

stages the subjacent bones may be extensively involved by direct spread of the tumour (Fig. 85).

Lupus carcinoma frequently develops at an earlier age than other forms of squamous-cell cancer of the skin. Its development often appears to be precipitated by irradiation by X-rays or radium.

Cancer in chronic ulcers of the skin occurs rarely. The growth usually appears at the edge of the ulcer. It takes the form of a hard, granular excavation which spreads very slowly in the surrounding skin and subcutaneous tissues, and may finally penetrate the adjacent bones. Spread to the regional lymph glands is a late occurrence because the lymph vessels have usually been obliterated by long-standing chronic lymphangitis.

Chronic leg ulcers, though very common lesions, are only rarely the seat of carcinoma.

(2) Basal-cell Carcinoma (RODENT ULCER).

This is an ulcerating tumour arising from the basal cells of the skin or from cells of similar derivation in hair follicles and sweat glands. It occupies a position intermediate between simple and malignant growths, for though locally invasive and destructive it extends very slowly and does not metastasize. It rarely occurs before

middle age, and males are affected more often than females. In the great majority of cases the tumour arises in the skin of the face, especially in close proximity to the medial or lateral palpebral commissure or in the naso-labial fold, less often in the frontal and temporal regions of the scalp. Tumours of similar character arise occasionally in the skin of other parts of the body, and sometimes in the squamous-cell mucous membranes, such as the tongue, pharynx and œsophagus.

At its inception the tumour lies deep to the epidermis, and at this stage may appear as a firm red papule or as a flat, slightly raised plaque. At an early stage, or rarely after a considerable period, the superficial epidermis gives way, and the growth then takes the form of an ulcer. Rarely two or three such ulcers may coexist.

The appearance of a rodent ulcer is characteristic. The surface is red and granular, and when small is usually covered by a dry crust or

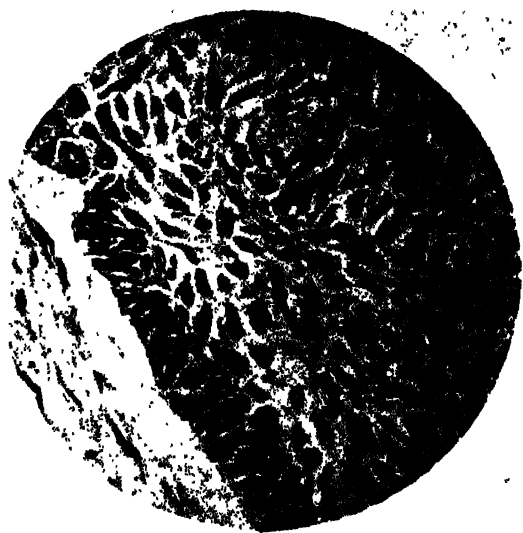


FIG. 29. Basal-cell carcinoma; rodent ulcer. High-power photograph of the edge of the tumour. $\times 450$. The tumour consists of masses of epithelial cells bounded by a single palisade row somewhat resembling the basal layer of the epidermis.

(Laboratory of Royal College of Physicians of Edinburgh.)

scab. (The edge may be smooth, regular, and cleanly cut, but often is slightly rolled or beaded.) It is not raised and thickened to the same extent as in a squamous-cell carcinoma. Around the edge and at the base of the ulcer there is generally a moderate amount of induration. Occasionally at one edge the erosion may be arrested temporarily, and a thin pellicle of young epidermis may grow in from the margin. Such a healing process is always very limited in extent and temporary, however, and in untreated cases it never prevails.

The spread of a basal-cell carcinoma is slow, but progressive. At first the tumour extends mainly at the expense of the surrounding skin and subcutaneous tissue, but later it involves deeper structures, which it invades, erodes and destroys. The regional lymph glands may

enlarge as a result of superadded infection, but metastases do not occur.¹ In a few well-authenticated cases malignant change has supervened. Such a change may follow inadequate irradiation therapy.

Microscopically, a basal-cell carcinoma is composed of epithelial cells disposed either in large, somewhat rounded masses, or in narrow columns and processes. Between and around the masses of cells is a stroma of richly cellular fibrous tissue, which is often infiltrated with lymphocytes and other inflammatory cells as a result of superadded



FIG. 30. A columnar-cell adenocarcinoma of the breast. $\times 100$. The acini vary in size and shape. They are lined by columnar cells, which in places are several layers deep. The supporting stroma is scanty and the blood vessels are thin walled.

(Laboratory of Royal College of Physicians of Edinburgh.)

infection. At first the tumour is covered by a thin layer of epidermis, and it is sometimes possible to trace a connexion between the deep surface of this layer and the epithelial cells of the tumour. Later, when the growth is ulcerated, the thinned-out epidermis is only visible at the edge.

The epithelial cells at the periphery of the cell masses are of low columnar shape, and are arranged in a single palisade layer, somewhat like the basal layer of the epidermis. The remainder of the cells, deep to this layer, are smaller, and polyhedral in shape.

A basal-cell carcinoma contains no cell nests and few prickly cells, an important feature which distinguishes it from squamous-cell carcinoma of the skin. Usually the cell masses are solid, but occasion-

ally there is an irregular adenomatous appearance, and degenerative changes may lead to the formation of small cystic spaces.

The origin of a basal-cell carcinoma is generally believed to be from the basal cells of the epidermis, but the adenomatous arrangement sometimes present has suggested that in some cases the epithelium of sweat glands or hair follicles provides a starting point. In view of the close morphogenetic relationship of these structures such a view appears quite reasonable.

(3) Glandular Carcinoma. This term is generally held to include tumours arising from columnar or cubical cells of mucous membranes and ducts as well as from the glandular elements themselves.

Glandular carcinoma occurs in many parts of the body. It is commonest in the breast, stomach and large intestine, but may occur in other parts of the alimentary tract, for example, the gall bladder, pancreas, liver, and in such organs as the ovary, uterus, prostate, kidney, adrenal gland and thyroid.

The cells of a glandular carcinoma may differentiate to the extent of reproducing, to greater or less degree, the acini of the gland, or they may form solid masses with no glandular architecture. Thus two types may be recognized :

(1) adenocarcinoma, in which there is some tendency to the formation of acini; and
(2) spheroidal cell carcinoma, in which no glandular structure recognizable.

Adenocarcinoma is commonest in the alimentary tract, but may occur in the other organs mentioned above. The acini are but imperfect reproductions of the glands from which they are derived, and they show many deviations from the normal. They vary greatly in size, and since they possess no ducts for evacuation of their content they become dilated with retained secretions, epithelial *débris*, etc. The lining membrane is no longer formed of a single layer of cells, but may be many cells deep, and having no basement membrane the cells tend to invade the subjacent stroma. The individual cells have the characteristics of malignancy and are large and deeply stained, and often show mitotic figures.

In some glandular tumours, *e.g.*, the ovary the thyroid, and occasion-

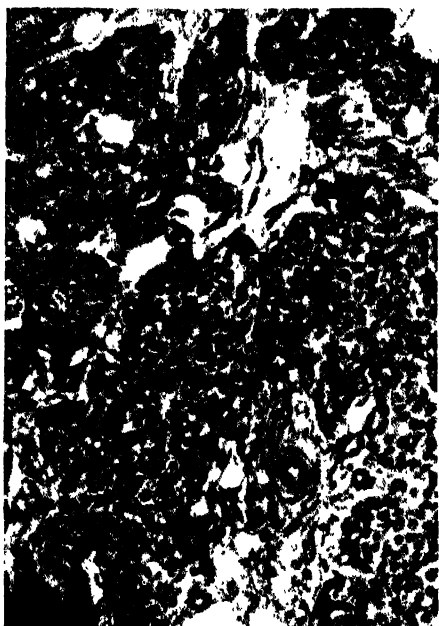


FIG. 31. Spheroidal-cell carcinoma of the breast.

(Department of Pathology, University of Glasgow)

ally the breast and kidney, the cells have a papillary arrangement—*papillary adenocarcinoma*.

In *spheroidal-cell carcinoma* the cells are arranged in solid, round, circumscribed masses with no glandular formation. This type of tumour occurs most often in the breast, less frequently in other glands. By mutual pressure the cells may assume polygonal shape.

Mucoid (Colloid) Carcinoma. This type of growth occurs most often in those regions where mucin-forming cells are normally present in large numbers, *e.g.*, in the stomach, colon, gall bladder, but they may occur elsewhere, for example, in the breast. The epithelial cells produce large quantities of mucin, which first distends the cells and then escapes into the intervening matrix. Eventually the greater part of the tumour may be replaced by mucin. The tumour is usually massive, with a characteristic semi-translucent appearance, and of soft, jelly-like consistency. Microscopically, the malignant cells are scanty, and of degenerate appearance, and the great bulk of the tumour is composed of clear gelatinous material.



FIG. 32. Mucoid cancer of the colon. Scanty epithelial cells lie in small groups separated by large quantities of mucoid material.

(Department of Surgery, University of Edinburgh.)

Mucoid carcinoma is generally believed to result from degenerative changes which may occur in any form of glandular carcinoma, but in certain features it differs entirely from ordinary forms of degeneration. Mucin is the specific secretion of the cells, and it occurs in metastases as well as in the primary tumour. Moreover, it has been shown in animals that the potentiality for this change may be transmitted through many generations of tumour. It

is often stated that mucoid degeneration is an index of a relatively low grade of malignancy, but there are many exceptions to this rule. In the breast, it is true, most mucoid carcinomata grow slowly and metastasize late, but occasionally breast tumours of this type are extremely invasive, and mucoid carcinoma of stomach, gall bladder and bowel tend to grow rapidly and spread widely.

MIXED TUMOURS

On previous pages it has been shown that practically all epithelial tumours, innocent or malignant, possess a stroma of connective tissue.

The term "mixed tumour," however, refers only to those growths in which both types of tissue are integral parts of the tumour, and participate equally in its neoplastic character.

It is believed that all the cells of a mixed tumour have a common ancestry from a single cell of embryonic type, which has retained its primitive capacity for producing different kinds of tissue. It is obvious that the more primitive the cell the greater its potentialities, and so there may be (1) multipotent cells capable of producing various kinds of mesodermic tissue (cartilage, muscle, bone, fibrous tissue, etc.) with or without glandular elements, and (2) totipotent cells capable of producing any or all types of cell or tissue.

Tumours arising from multipotent cells occur most often in the kidney and the testis and ovary, and are considered in detail in the chapters devoted to those organs. A tumour derived from totipotent cells is generally known as *teratoma*, less often an *embryoma*.

Teratoma. This term should be restricted to tumours derived from totipotent cells, and should not be used to include mixed tumours of less complicated type, such as occur in the kidney or salivary glands.

There are two distinct classes of teratoma: (1) those recognizable at birth, and usually situated close to the surface of the body; (2) those appearing after birth or in adult life, and usually affecting internal organs.

A teratoma recognizable at birth represents incomplete uniovular twins. It is usually situated in the sacro-coccygeal region, and projects on the surface of the autosome. Sometimes it takes the form of complete limbs or of parasitic twins in various degrees of perfection. The most extreme examples are the fully formed conjoined twins, which may be regarded as mutual teratomata. In other cases a congenital teratoma is a shapeless mass containing in irregular confusion a great variety of tissues or portions of organs. Such masses are commonest in the sacral region but may occur in the region of the upper jaw, and the term *epignathus* may then be applied.

A teratoma developing after birth or in adult life is found most often in the ovary or the testis, but it may occur in other situations, for example, the brain, mediastinum, or the retroperitoneal tissues (*extragenital teratoma*). It has been suggested that it arises from parthenogenetic development of germ cells, but it seems more probable that the origin is from blastomeres, or from undifferentiated germ cells, totipotential cells derived from the early embryo, which have been sequestered or remained inactive during development.

The tumour may be either solid or cystic, and it may contain tissues derived from all three embryonic layers. (Stratified squamous epithelium, sebaceous glands, hair follicles and enamel organs) lie irregularly disposed among masses of cartilage, bone, and muscle; and various gland-like structures lined by columnar epithelium are also present. Even Langhans cells and the *syncytium of chorionic epithelium* occur, and occasionally they may constitute the greater part of the tumour, even when it is situated in the testis.

Ovarian teratoma is often cystic. It is sometimes known as ovarian dermoid, for it may resemble an inclusion dermoid cyst.

There is a large cavity containing hair and sebaceous matter, and projecting from the wall of the cavity may be a hard plaque covered with skin and often containing teeth. An ovarian teratoma differs from inclusion dermoids in possessing tissues derived from all the three primary layers, and in addition to skin derivatives it contains muscle, cartilage, glandular structures, and even thyroid tissue and nerve cells.

Teratomata are not necessarily malignant tumours, and some of them, especially those situated in the ovary, remain stationary for many years or only enlarge by the distension of their cystic spaces. Others, however, notably teratomata in the testis, are usually very malignant. The malignant change may affect one or several of the

constituent tissues, though not always in equal degrees.

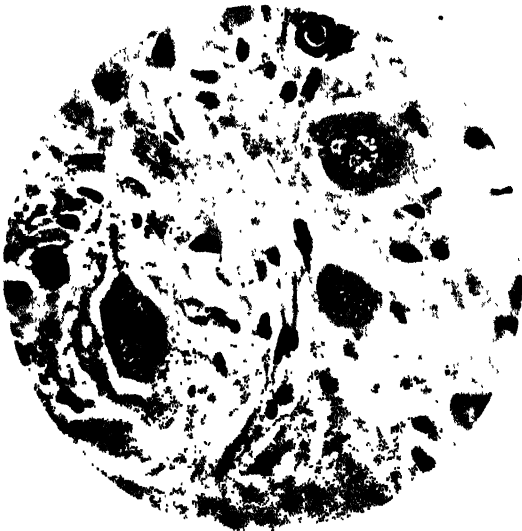


FIG. 33. Ganglioneuroma. $\times 300$. The tumour was situated in the retroperitoneal tissue. Note the characteristic ganglion cells, unipolar and bipolar. Nerve fibres also are present, and small cells of neurilemma type.

(Laboratory of Royal College of Physicians of Edinburgh.)

TUMOURS DERIVED FROM NERVE TISSUE

Tumours of nerve tissue may arise in the central nervous system, in peripheral nerves, in the trunks and ganglia of the autonomic system, and in various tissues such as the adrenal medulla, which are closely allied developmentally and functionally to that system.

In the brain and spinal cord the common tumours arise from the supporting fabric (neuroglia) and only very rarely from the nerve cells. *Gliomata* present many different types, according to the degree of differentiation of the predominating cells, and they may grow slowly or with extreme rapidity. They are considered fully on p. 277. True tumours of the peripheral nerves are extremely rare. It is possible that the acoustic neuroma is a true tumour of nerve tissue, and its characteristics are considered in detail on p. 284. The tumours commonly called neurofibroma or false neuroma are not derived from nerve tissue but from the neurolemma sheaths of nerves. The so-called amputation neuroma or stump neuroma is merely hyperplasia of the cut nerve fibres (see p. 321).

Tumours of autonomic nerves form an interesting group of new growths, which have been more clearly recognized in recent years. Formerly they were confused with sarcoma, to which they bear great

resemblance. They are the commonest malignant tumours in infants. Tumours of this class arise from the ganglia of the autonomic system and they are most commonly situated in the retroperitoneal tissue and in the mediastinum. They arise not from neuroglia but from the embryonic nerve cells (sympathicoblasts). Most often the cells are of immature type, hardly recognizable as nerve cells, and the terms *sympathicoblastoma* or *neuroblastoma* may then be applied. Such tumours commonly occur in infants or young children, and grow rapidly and metastasize widely. Less commonly the cells are fully differentiated and resemble the ganglion cells of the autonomic system. Such tumours, *ganglioneuroma*, take a benign course. Either neuroblastoma or ganglioneuroma may also arise from the adrenal medulla, a tissue closely related in origin and function to the autonomic nervous system (*see* p. 601). Tumours similar to a neuroblastoma may arise in the retina from the primitive cells of the central nervous system. They are usually of familial incidence and arise in infancy or early childhood.

In recent years certain tumours have been described which are believed to take origin in chromaffin tissues in various parts of the body. The most outstanding examples of such tumours, which have been termed *paraganglioma*, are the tumour of the carotid glomus, and the chromaffinoma of the adrenal medulla.

TUMOURS DERIVED FROM ENDOTHELIUM

Until the last decade endothelial tumours were generally believed to be of common occurrence, but with stricter pathological criteria in the recognition of endothelial cells it is now clear that this was a mistaken view. Endothelium forms the lining membrane of blood vessels and lymph vessels, and the pleura, pericardium and peritoneum. But with the exception of hæmangioma and lymphangioma, primary tumours of these tissues are extremely rare. Tumours of the pleura or peritoneum, for example, are almost invariably secondary to some growth, perhaps of very small size, of the underlying viscera or in distant situations. And the so-called dural endothelioma is now believed to arise from the arachnoid mater, which is not considered to be an endothelial structure.

Tumours of the endothelium of blood vessels and lymph vessels are described on p. 255 and 256.

✓ MELANOMA

PHYSIOLOGY OF PIGMENTATION

The dark races owe the colour of their skin to the pigment melanin, and in them it affords protection for the underlying structures against the powerful rays of the sun. The pigment is most abundant in the basal layers of the epidermis, but it may be present as high as the stratum granulosum or even the stratum corneum. In the fair races pigmentation is present only in the skin of the nipple, the axilla and the ano-genital region ; but in the foetus the basal layer of the skin in other

parts of the body is pigmented and becomes depigmented soon after birth. The capacity for pigmentation, however, is retained in adult life, and under the action of intense sunlight or ultra-violet irradiation the skin becomes bronzed or freckled, and it is then noted that the deeper layers of the epidermis acquire melanin pigment, and that the stratum corneum becomes deeper. As the sunburn or freckling disappears the cells slowly give up their pigment. In the pigmented basal cells melanin is distributed in the form of brown or black granules of fairly uniform size which are aggregated around the upper pole of the cell nucleus.

In the basal layer there are, in addition, pigmented cells of a *dendritic* type, and these are present in greatest number when a stimulus to pigment formation, such as sunlight, X-rays, or ultra-violet radiation, is applied to the skin. As transition forms between this type of cell and the ordinary basal cells can be traced, it is believed that they are derived from normal basal cells, and that the assumption of dendritic processes is evidence of an active phase of pigment formation. Their origin from basal cells is also substantiated by their specific staining qualities (*see below*).

Pigmented cells of somewhat similar appearance are also found constantly in the dermis, (especially around the blood vessels). The origin and function of these cells has given rise to considerable discussion. From their peculiar staining affinities it is believed that they arise from the connective tissue of the corium, and that they are not specifically concerned with the elaboration of melanin, but with its disposal, and for this reason they have been termed *chromatophores*. The pigment in the cells is in the form of irregular globules, and it is believed that they acquire it from the epidermis.

Apart from the skin, melanin occurs in the pigmented structures of the eye (retina, chorioid, iris, and ciliary body). In the central nervous system it is found in the substantia nigra and, in varying amounts, in the meninges.

Melanin is the only pigment normally found in the skin of man. It is elaborated by cells of the epidermis, and the cells with this property are known as *melanoblasts*. Melanin contains no iron in its complex molecule, and hæmoglobin plays no part in its formation; sulphur is present, probably only as an impurity. The ultimate source of melanin, like adrenalin, is *tyrosin*. In lower animals, melanin is formed in the cells of the epidermis directly from tyrosin, through the action of a ferment or oxydase—*tyrosinase*. In higher animals, however, the process is more complicated, and before reaching the pigment-forming cells, tyrosin is converted into a colourless chromogenic substance known as dihydroxyphenylalanine (D.O.P.A.). This substance, on reaching the pigment-forming cells, is converted to melanin by a specific intracellular ferment, called by Bloch *dopa-oxydase*.

The conversion of *dopa* into melanin in the melanoblasts may be demonstrated *in vitro*. Bloch demonstrated that sections of skin soaked in a solution of *dopa* showed deposition of melanin in only those strata in which pigment formation normally occurs (*viz.*, the deeper layers of the epidermis), and this behaviour of the skin is known as the *dopa*

reaction. It is likely that the *dopa* reaction resembles very closely, or is identical with, the normal process of melanogenesis. The reaction is only evidenced in those cells in which *dopa*-oxydase is present, *i.e.*, in cells that are melanoblastic, actively or potentially; and the results suggest that melanin formation is almost entirely a function of tissues derived from ectoderm, and of the skin in particular.

When *dopa* is applied to frozen sections of human skin the basal layers become blackened, due to the deposition of granules of melanin in the cytoplasm of the cells, and the intensity of pigment production coincides with the existing amount of pigment present in the skin examined. The dendritic cells of the epidermis, referred to above, also show a positive *dopa* reaction, but the pigmented branched cells of the corium (melanophores) are *dopa* negative. This observation is held to prove that the melanophores are not of epidermal origin, and that they do not produce, but merely carry pigment.)

In some pathological states there may be generalized or localized diminution of pigmentation of the skin, in others there may be an increase. In **albinism**, there is total absence of melanin from the skin, hair and eye, and the *dopa* reaction of these structures is negative. In **vitiligo**, the reaction is negative in the depigmented areas of the skin, and is strongly positive in the adjacent zones of hyperpigmentation. In **Addison's disease**, brown pigmentation may be uniformly distributed throughout the skin surfaces of the body, or it may be relatively excessive in certain areas.

It is believed that the precursor of adrenalin is identical with *dopa*, and that when the suprarenal glands are diseased they are unable to utilize their normal quota of the mother substance; therefore, it is surmised, the pigmentation of the skin is evidence of a compensatory action of the melanoblasts to utilize the excess of chromogenic substance in the body. Accordingly, the *dopa* reaction of the skin in Addison's disease is weak, because the *dopa* oxydase has already been utilized in the formation of melanin pigment.

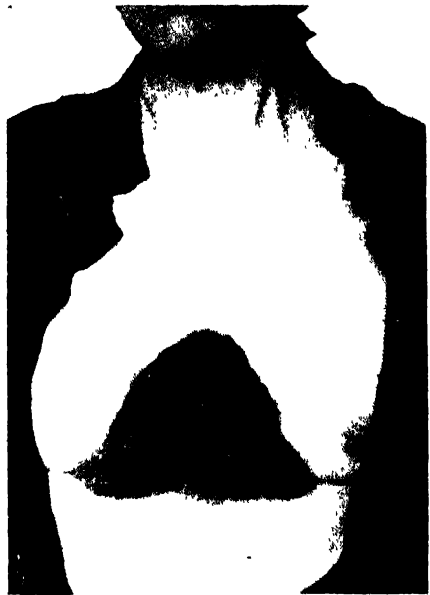


FIG. 34. Symmetrical melanoma of front of chest.
(Museum of Royal College of Surgeons of Edinburgh.)

TYPES OF MELANOMA

A melanotic tumour or melanoma arises most often in the skin, rarely in the eye or in other parts of the body. It is usually present at

birth, and the term *nævus* (Latin: *nævus*—a birthmark or blemish) may be applied to it; less commonly, it becomes obvious about puberty, or in adult life. There is evidence that a melanoma may result from trauma.

A congenital melanoma is represented in simplest form by a flat or slightly raised pigmented spot or macule. When more pronounced it may take the form of a warty, pedunculated, or hairy mole. Sometimes tumours of this class are very numerous and may be disposed in groups or in irregular lines (systematized and linear melanoma). Occasionally they form large diffuse patches, sometimes distributed symmetrically on the trunk or limbs (giant melanoma). The "bathing trunk" pattern of diffuse pigmentation, sometimes found in association with generalized neurofibromatosis, is an exaggerated example of this variety.



FIG. 35. Secondarily pigmented melanoma of acanthotic and keratoid types. The pigmentation is confined to the epidermis, and there are no epithelial cells in the corium.

(Laboratory of Royal College of Physicians, Edinburgh.)

Most melanomata are simple tumours and remain so throughout life; but some, after remaining unchanged during many years, may enlarge and show signs of malignancy; and occasionally a melanoma is malignant from its onset. According to these modes of behaviour, the melanomata may be described conveniently under three headings: (1) benign melanoma, (2) malignant melanoma arising in benign growths, (3) malignant melanoma arising *de novo*.

(1) Benign Melanoma

Two main types of benign melanoma may be recognized: (a) the "hard" or secondarily pigmented melanoma, (b) the "soft" or *nævus-cell* melanoma. The two types can be distinguished only by histological examination, and the essential difference is that in the former type, the (secondarily pigmented melanoma, the pigmented cells lie entirely within the epidermis), whereas in the latter type some of the characteristic cells of the tumour, the so-called *nævus* cells, lie deep to the epidermis in the corium.)

"Hard" or Secondarily Pigmented Melanoma. This should be regarded as warty growth which is pigmented, and in which the pigment appears to play an entirely subordinate rôle. It is pedunculated or sessile and may be discrete or aggregated. It may arise from the stratum corneum of the epidermis (*keratoid type*), or from the

prickle-cell layer (*acanthotic type*). These tumours differ from other forms of melanoma in that they seldom become malignant, and that, when they do, they give rise to typical squamous-cell carcinoma, not to malignant melanoma.)

Soft or "Nævus-cell" Melanoma. This tumour consists of aggregations of cells in the deeper layers of the epidermis as well as in the corium. The cells in the epidermis are usually elliptical and non-fibrillated, and are arranged in groups or cell nests, which cause expansion of the rete processes of the epidermis.

[The cells in the corium are round, mostly non-pigmented, and arranged in regular groups or columns. These cells are known as *nævus cells* and they are characteristic of this type of tumour. The *nævus cells* are separated from one another, and from the epidermis, by a variable amount of connective tissue. The cells are of spherical shape, with scanty cytoplasm and a round or oval nucleus which has a definite



FIG. 36. Benign nævus-cell melanoma. Note the groups of nævus cells regularly arranged in the upper part of the corium and the thickening of the overlying epidermis.

(Laboratory of Royal College of Physicians of Edinburgh.)

nucleolus and a clear chromatin network. They show a faintly positive dopa reaction, and are, therefore, presumed to be capable of melanin formation. At the periphery of the columns of nævus cells and in the adjacent tissue there are a few pigmented granular cells of branching or rounded shape which are believed to be ordinary phagocytic cells containing pigment (melanophores). In a few cases of nævus-cell melanoma the histological changes are confined to the epidermis.

The problems of melanoma and the exact origin of the nævus cell are very complex and do not admit of dogmatic answers. The histological interpretations are difficult and uncertain. The various views may be classified thus: (1) the nævus cells are mesodermal in origin, and arise from the endothelium of lymph and blood channels (Von Recklinghausen), or from undifferentiated connective tissue cells (Ribbert); (2) they are epidermal in origin, and arise from specific cells—melanoblasts (Unna, Dawson); and (3) they are related in their origin to the terminal nerve fibres of the skin (Soldan, Masson, Ewing).*

Dawson, from elaborate histological studies, adduced strong evidence to uphold the epidermal origin of the nævus cell. He was able, from a large series of sections, to trace the processes by which they arose from

localized areas of pigmented cells in the deeper layers of the epidermis. He stated that, "the process could be traced from the localized areas of pigmentation of the basal cells, through a series of cell transformations occurring in those cells, to the formation of intra-epidermal cell nests"; and that, "in the intra-epidermal formations the epithelial cell, having lost its intercellular fibrils, becomes detached and actively proliferative, assumes a spindle or star-shaped form, till finally the cell group or its component cells break through the transition zone between epidermis and corium, leaving the superficial layers to heal up, while they themselves migrate and settle in the upper corium, where they undergo regressive processes, and become the atrophic cells of the nævus. They arise, however, as melanoblasts and remain potential melanoblasts, though they become depigmented and give up their pigment to chromatophores on the periphery of the cell groups."

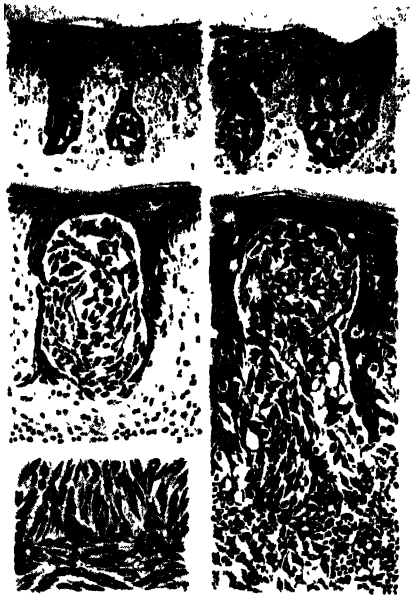


FIG. 37. Stages of evolution of a malignant melanoma.

(Laboratory of Royal College of Physicians of Edinburgh.)



FIG. 38. Simple melanoma showing malignant transformation. Note the melanoblasts "spraying" from the rete processes and also the irregularity of the nævus cells in the upper corium.

(Laboratory of Royal College of Physicians of Edinburgh.)

The researches of Masson, which have been amplified by Ewing, afford equally strong evidence that the nævus cell is a derivative of specialized cells found in association with the sensory nerve ends in the corium or in the epidermis, or in both. Their views have now gained general support; they certainly offer a simple explanation of the pigment changes found in neuro-fibromatosis—itself a disease affecting

specially neuro-ectodermal structures—suggesting the active participation of epithelium in a melanoma may be referred to the growth of specialized cells belonging to the nerve-end apparatus.

(2) Malignant Melanoma (Arising in a Benign Growth)

The presence of melanin in the cells of a simple melanoma appears to lead to a state of instability and a tendency to malignancy. It is sometimes observed that a benign melanoma that has remained unchanged during many years unexpectedly shows enlargement, increased vascularity and finally malignancy. The change may occur spontaneously, or it may be initiated by trauma. The signs of malignant change may appear gradually, or they may occur with great suddenness, manifest by rapid local infiltration, enlargement of lymph glands, or the appearance of metastases. In other cases evidence of malignant change is evidenced by local recurrence after removal of an apparently simple growth. It is important to realize that increase in size may be an inconspicuous feature of malignant transformation, for, in some sites, such as the nail bed and the eyeball, the tumour may be extremely small, and may have escaped detection, and, in such cases, widespread metastases often occur without apparent enlargement of the primary growth.

Transition to malignancy in a benign melanoma appears to be a dual process and is caused by proliferation of the quiescent naevus cells and the multiplication of new cells derived from the surface epithelium, especially the rete processes. Histologically, these changes are marked by the appearance of larger protoplasmic forms of "naevus cells," which often show two nuclei. These cells tend to become free from the pre-existing cell groups and to form isolated masses. Coincidentally with these changes the rete processes in the epidermis increase in number over a variable distance, and they become broad and club-shaped, due to proliferation of the cells within them. At



FIG. 39. Melanoma involving the scapula. A metastasis which developed eighteen years after removal of an ocular melanoma.

(Department of Surgery, University of Edinburgh.)

different parts the rete processes rupture, and pale protoplasmic cells penetrate into the corium, where they proliferate and give rise to stellate or spindle-shaped forms with a variable degree of pigment (see Fig. 87).

(8) Malignant Melanoma (Arising de novo)

A malignant melanoma may occur at almost any point on the surface of the body, but common sites are the forehead, the neck, the abdominal wall, and a nail fold (The nail fold or bed is the commonest of all). In some sites the primary tumour remains small although metastases may be numerous; in others the tumour may grow rapidly to a large size and may ulcerate.



In general, a malignant melanoma may be regarded as the most aggressive of all tumours. It has pronounced infiltrating characters and therefore spreads widely by direct extension. In addition, it tends to invade the lymph vessels, giving rise to metastases in the regional lymph glands. The tumour cells may actually grow in the lymph vessels and give rise to multiple and/or massive secondary growths in their course. The secondary deposits in the lymph glands are frequently more deeply pigmented than the primary growth.

In many cases a malignant melanoma metastasizes by the blood stream and gives rise to multiple secondary growths in the lungs, brain, liver, kidney, and skin. Metastases may be so numerous and widespread that the condition is known as generalized melanosis. In a few cases the secondary tumours are non-pigmented or only pigmented in patches. A tendency to spontaneous retrogression of the metastases has been observed in a few instances. In a few instances of generalized melanosis careful search has failed to reveal the primary focus. In some instances a metastatic tumour does not come to light until many years after the removal of the primary growth (see Fig. 89).

FIG. 40. Small ocular melanoma with multiple secondary nodules in the liver. Some of the nodules are non-pigmented.

(Department of Pathology, University of Edinburgh.)

Histologically, the most striking feature of the malignant melanomata is the diversity of their structure, and according to the form and configuration of the cells they may be divided into three main groups: (1) melano-carcinoma, in which cells of epithelial character are arranged in alveoli; (2) the melano-sarcoma, composed of spindle cells; and (3) melano-endothelioma. Transitional forms may occur or there may be striking variations within the same tumour.

Ocular melanoma arises from those parts of the eye which normally contain pigment. It occurs most often in the conjunctiva, the chorioid, and the pigmented layers of the retina, and more rarely in the iris and ciliary body. Usually it is highly malignant.

Melanoma of the bulbar conjunctiva does not differ greatly from one in the skin. It forms a flat diffuse growth which often overlies part of the cornea. It tends to recur after operation, and removal of the eye may be necessary for its eradication.

The intra-ocular melanomata are of two varieties ; (a) circumscribed, and (b) diffuse.

(a) *The circumscribed tumour* is often lenticular in shape. It usually occurs in the chorioid, from which it tends to spread to the subretinal space, and then assumes a mushroom shape. The sclera resists invasion for a considerable time, and, as a result, there is great disorganization of the interior of the eye. After the sclera is infiltrated extension to the perforating arteries or the optic nerve occurs. Metastases, usually in the liver and lungs, may develop while the primary growth is exceedingly small. Local recurrence after removal of the eyeball is not common.

Histologically, this type of tumour shows great structural variations (polymorphism), not only in the different tumours, but in the same tumour. The commonest appearance is that of a pigmented spindle- or round-cell sarcoma. Pigmentation is irregular and may only be present in groups of cells, or the pigment may lie in clumps between cells.

(b) *The diffuse tumour* is characterized by longer duration of growth and by a greater tendency to spread by the perivascular lymph channels. The cells in this type are polygonal or spindle-shaped and vary considerably in their pigmentation.

Dawson claimed that all the ocular melanomata were of epithelial origin, and that the histogenesis was the same as in melanotic tumours of the skin. He based his claims on the essential structural similarity of the skin and the conjunctiva, and on the neuroectodermal origin of the normal pigmented cells of the retina and choroid.

IRRADIATION OF TUMOURS

The increasing use of X-rays and radium in the treatment of tumours makes it imperative for the surgeon to be familiar with the pathological results which may follow excessive dosage by these types of irradiation.

In general, the effects of X-rays and of the gamma rays of radium are similar, except that X-rays, being necessarily applied externally, have their maximum effect upon the integument, whereas radium if introduced below the surface acts principally upon the tissues immediately around it. The disturbance may be constitutional or local, and in either case may be acute or chronic. Acute effects are seen in patients as a result of excessive exposure to the rays, whereas chronic effects occur usually in radiologists, the result of prolonged and repeated irradiation.

Constitutional Effects of Irradiation. Acute constitutional disturbance is manifest within a few hours or a few days of the time of

irradiation. When mild, it is characterized by headache, malaise, anorexia and nausea ; when severe, it may lead to vomiting, diarrhoea, prostration and death. The toxæmia responsible for these manifestations has been attributed variously to acidosis, alkalosis, destruction of the white blood cells, disintegration of lecithin, derangement of the colloidal equilibrium, and alterations in the chloride distribution in the body fluids.

Chronic constitutional effects are characterized principally by degenerative changes in the blood-forming tissues. Secondary anæmia develops, with leucopenia and a relative lymphocytosis. Sometimes leukæmia or aplastic anæmia supervenes.

Local Effects of Irradiation. The local effects of irradiation vary greatly, depending, on the one hand, upon the intensity and duration of the exposure and, on the other, upon the radiosensitivity of the tissues. The radiosensitivity is a variable factor, for it depends not only upon the type of cells but also upon their state of activity at the time of irradiation. In general, the most sensitive of normal cells are the germ cells, the lymphocytes, and the highly specialized parenchymatous cells of viscera, especially the liver, spleen, thyroid gland and bone marrow. All cells are most sensitive during growth and multiplication. These facts form the basis for clinical therapy in certain non-malignant diseases. Thus treatment by X-ray or radium is valuable in certain forms of hyper-thyroidism and in some disorders of the spleen and bone marrow. It also affords relief in certain inflammatory conditions, for example, dermatitis, diverticulitis and rheumatoid arthritis, although its mode of action in these diseases is not understood.

The local action of irradiation has been investigated more thoroughly in the skin than elsewhere. When the skin is exposed to a single "overdose" of irradiation it may exhibit any degree of damage from a mild erythema to a deep burn. These effects are usually not manifest until several days after the exposure. Irradiation burns are characterized by a tendency to continue unhealed during long periods, for the irradiation effects an obliterative endarteritis with fibrosis of the surrounding tissues, and consequently the sloughs are slow in separating and the processes of repair are delayed.

If insufficient to produce such acute effects the irradiation may result in changes that become manifest only after a period of weeks or months. The cells of the hair follicles and sweat glands are often destroyed, and consequently the hair subsequently falls out and the skin becomes dry and shiny. Often the skin becomes deeply pigmented.

Repeated irradiation of the skin may give rise to chronic dermatitis, and this may lead to an "irradiation carcinoma" (X-ray carcinoma). Such effects are almost limited to radiologists, and, as a consequence of the former practice of holding the fluorescent screen in the unprotected hands, they are situated most often on the dorsal aspect of the fingers. It is interesting to note that an irradiation burn such as results from simple overdosage shows no special liability to the development of malignant disease. The chronic skin lesions are due essentially to endarteritis obliterans, perivascular fibrosis, and œdema of the cutis vera, as well as to secondary changes in the epidermis. The nails become

corrugated and brittle, and eventually separate from the matrix. The skin becomes red, shiny and atrophic, and later pale, dry and thickened. Sometimes ulcers develop, which tend to penetrate deeply and to remain unhealed during long periods. Later, multiple papules and warty nodules appear, the harbingers of cancer.

Irradiation cancer arises usually on the basis of one of the warty nodules. It occurs as a late manifestation, and may develop many years after the final exposure to irradiation. In some cases two or more independent carcinomata arise. The growth has the microscopic characters of a squamous-cell carcinoma, but since the tissue is fibrous and the lymph vessels are extensively obliterated the growth spreads slowly and metastasizes late.

Effects of Irradiation on Tumours. In accordance with the general concept that the radiosensitivity of cells varies according to their activity, tumour cells are generally more susceptible to irradiation than normal cells, and the cells of malignant tumours are generally more susceptible than those of simple tumours.

If a radium needle be implanted in a tumour, its effects vary in different parts of the tumour inversely as the square of the distance. Immediately around the needle the tissue, both cells and stroma, rapidly undergoes necrosis, and eventually forms sloughs, small or large according to the dosage. In the zone peripheral to this area the cells undergo a form of coagulation necrosis and are destroyed, but the stroma, being less vegetative, survives, and consequently no gross sloughing occurs. In a zone more peripheral still from the needle, the rays destroy only a certain proportion of the tumour cells, more particularly those in mitotic division at the time. Other cells, not destroyed, are believed to be subjected to inhibitory influences which have the effect of restraining their growth.

In irradiation therapy the aim is to effect maximum tumour destruction with minimum damage to the normal tissues. This object is achieved by accurate estimation of suitable dosage and careful distribution of the needles so as to attain a uniform field. It is generally believed that successful treatment is enhanced by the use of relatively small amounts of radium over a long period, which ensures that during the time of irradiation a greater number of malignant cells will enter the phase of mitosis and thus become especially vulnerable.

The above-mentioned effects of irradiation upon tumours relate to the cells of the tumours. It must be observed, however, that the stroma also is affected. The rays cause thrombosis of the blood and give rise to an obliterative endarteritis, and subsequently they lead to fibrosis and obstruction of the lymph vessels. Thus they reduce the vascularity of the tumour, interfere with the nutrition of the tumour cells, and delay or inhibit extension. In some cases the irradiation gives rise to a local infiltration by lymphocytes, plasma cells and eosinophil leucocytes, and these may possibly have some antagonistic effect upon the invading malignant cells.

Radium Poisoning. Poisoning by ingested radium has occurred in a few instances, notably in Orange City, New Jersey, where girls employed in painting clock dials with luminous paint were affected.

The pigment used for this purpose contained minute amounts of radium, together with mesothorium and radiothorium, and the poisoning was due to the ingestion of these substances from licking the paint brushes. After absorption, the radium and thorium compounds are stored in cells of the reticulo-endothelial system, particularly in the bone marrow, and remaining there permanently they discharge alpha particles and exert a profound effect upon neighbouring cells. At an early stage they give rise to a "radiation osteitis," characterized by increasing sclerosis of the bones. If oral sepsis coexists, necrosis of the jaw is a common result. Later, sometimes several years after absorption of radium has ceased, there is a liability to various forms of anæmia and leukæmia, which may prove fatal.

An extremely interesting late effect of radium poisoning is the development of bone sarcoma, generally of a rapidly growing, cellular type. It appears that the long continued irritative action of the radium, first manifest in a proliferative osteitis, eventually predisposes the cells to neoplastic hyperplasia.

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CHAPTER VIII

DISEASES OF BONES

THE problems of osteogenesis, normal and pathological, remain the subject of unabated controversy. Bone has been described as a connective tissue impregnated with lime salts, but, though true enough, this simple statement gives no indication of the complicated structure of bone, so beautifully adapted and adaptable to bodily needs, nor of its manifold functions in relation to metabolism and its responses to hormonal influences. These anatomical and physiological considerations have such a close bearing upon the pathology of bone diseases as to necessitate a detailed account of them.

ANATOMY OF BONE

For illustration a typical long bone will be considered. Such a bone consists of a shaft or *diaphysis* and of two extremities or *epiphyses*. During the period of growth the diaphysis is separated from the epiphyses by plates of hyaline cartilage, the *epiphysial cartilages*. Some bones possess, in addition, secondary epiphyses or *apophyses*, which are separated from the diaphysis or the primary epiphyses by plates of cartilage.

From the pathological standpoint the most important part of a bone is the *metaphysis*, the region of cancellous bone immediately on the diaphysial side of the epiphysial cartilage. This is the region from which all lengthwise growth of bone proceeds, it is the most vascular region of the bone, and it is the region most liable to injury. For these reasons it is especially apt to be involved in trauma or in infective disease in childhood or adolescence, and it is especially affected by any interference with the normal processes of calcification and ossification during those periods. It is also the region most subject to tumour formation.

Blood Supply. The distribution of blood vessels in bones is of importance in determining the sites affected by disease.

In a typical long bone the sources of blood supply may be classified as follows: (1) The nutrient artery, (2) periosteal arteries, (3) metaphysial (juxta-epiphysial) and epiphysial arteries.

(1) *The nutrient artery* is a vessel of considerable size, which supplies the major portion of the bone. It enters the bone usually at its middle third, in a direction obliquely away from the larger metaphysis. Inside the bone the artery divides into two principal groups of vessels, which are directed in the long axis of the bone towards either end of the shaft. They terminate at the metaphysis by anastomosing with other vessels to be described below.

(2) *The periosteal arteries* are fine twigs which supply the superficial layers of the cortex of all parts of the bone. They are large and abundant in childhood, scanty and small in old age.

(3) *The metaphysial (juxta-epiphysial) and the epiphysial arteries* are fine vessels derived from the arterial plexus (the *circulus vasculosus* of Hunter) which form a network encircling the bone in close relation to the joint capsule. These vessels penetrate the periosteum and cortex to reach the metaphysis and epiphysis respectively, and they terminate by anastomosing with the terminal branches of the main nutrient artery. Thus it will be seen that the metaphysis, the region of maximum bone growth, is supplied by three sets of blood vessels: (1) terminal branches derived from the main nutrient artery; (2) metaphysial arteries; (3) epiphysial arteries that have penetrated the epiphysial cartilage. These anastomosing vessels at the metaphysis are large and tortuous, and consequently at this region the blood flows slowly and any blood-borne organisms are apt to be arrested.

The above description applies to typical long bones. In short and irregular bones the blood supply is somewhat different, and is derived principally from periosteal arteries, and to a less extent from one or more "nutrient" arteries. In the short long bones of the hand and foot the blood supply is derived principally from single nutrient arteries, which pierce the shaft and immediately break up into fine twigs. In infancy these bones possess no metaphyses, and consequently diseases such as tuberculosis originate in the centre of the shaft.

Microscopic Structure of Bone. All parts of a bone are pervaded by channels of various sizes, relatively few in compact bone, numerous in cancellous bone. The large channels are the *Haversian canals*. These run mainly in the long axis of the bone, and they contain connective tissue, blood vessels, nerve filaments, and lymph channels. In addition, the large channels of cancellous bone contain marrow elements. Around the Haversian canals and communicating with them are the *lacunæ*, which contain the bone cells, the branched cells of the connective tissue framework which preside over the nutrition and metabolism of the bone. The branching processes of these cells occupy minute channels or *canaliculi*, which ramify in all parts of the bone.

Around each Haversian canal the bone is arranged in concentric lamellæ, which with the canal, the lacunæ and their canaliculi constitute a *Haversian system*. Near the surface of the bone a different arrangement obtains. The lamellæ here lie parallel to the surface and are nourished by blood vessels of periosteal origin lying in the Volkmann's canals. These superficial lamellæ are pierced by perforating fibres of white fibrous and elastic tissue, which are connected with the periosteum and with the insertions of tendons and ligaments.

It will be noted how admirably a bone is constructed for its essential function of providing a rigid support. The Haversian systems arranged longitudinally, and the superficial lamellæ arranged parallel to the surface, give longitudinal stability, whilst the fibrous and elastic tissues give elasticity and strength. Bone may be compared to a plaster of Paris bandage, in which the gauze is represented by the fibrous and

cellular parts of the bone and the plaster by the calcareous part. Incinerate a bone and only the calcareous material is left; place it in strong mineral acids and only the fibrous structure remains.

It should be observed that in spite of its hardness and density bone is a very vascular tissue, unlike that other component of the skeleton, cartilage. It is for this reason that bone so readily undergoes decalcification or other changes in response to metabolic or hormonal influences, or from the effects of local lesions such as tumours, aneurysms, or infections.

THE GROWTH OF BONE

The majority of bones are formed in cartilage, and only a few, including the bones of the calvarium and some of the facial bones, are developed in membrane. Since bone formed in cartilage is especially subject to diseases, the process of endochondral ossification will be described in some detail.

Bone formation starts in the clavicle in the fifth week of intra-uterine life, and in many other bones a short time later. The ossifying process begins near the midpoint of the bone and spreads thence through the whole diaphysis. Secondary centres of ossification appear later in the epiphyses and apophyses, and later fuse with the shaft.

Microscopically, in the process of ossification several distinct changes may be recognized, whereby the cartilage first proliferates, then becomes calcified, and finally is replaced by vascular bone-forming connective tissue. The cartilage itself is not ossified; it merely provides a cellular matrix suitable for the growth of osteogenic connective tissue. The stages of bone formation may be recognized as three distinct zones in a growing bone, extending from the pre-formed hyaline cartilage at one end to the completed bone at the other. The first zone is the *zone of proliferation of cartilage*. The cartilage cells increase in number and in size, and they become arranged in columns disposed in the long axis of the bone. The number of columns is constant in each bone. The second zone is the *zone of provisional calcification*, where calcium phosphate is deposited from the blood stream forming a narrow band extending the whole width of the bone, so that when the bone is cut longitudinally it appears as a thin white transverse line. In diseases associated with deficient calcification this white line may be absent or replaced by a broad irregular area of greyish colour. The third zone is the *zone of replacement of cartilage by osteogenic tissue*. Capillary vessels grow out in regular columns from vessels in the existing bone into the band of calcified cartilage, and the new bone is formed around and between these vessels. Along with the vessels come small dark-staining cells or osteoblasts. These are specialized connective-tissue cells which are generally regarded as the specific bone-forming cells; their function being to elaborate an osteoid matrix in which calcium is deposited to produce bone as we recognize it. When the bone has been formed the osteoblasts remain as "bone cells."

THE REMODELLING PROCESS

Bone is not an inert and immutable framework, but a living tissue adjusted to meet the varied forces imposed upon it. This is evidenced most strikingly during growth of the skeleton. The primordial bone at the metaphysis is relatively soft and vascular, and is not fitted to meet the stresses imposed by gravity and muscular action. It is adapted to these requirements by a process known as remodelling, by which the bone becomes compact or cancellous according to the functional requirements of the part. The remodelling process is the factor that decides the ratio between size, stability and strength in bones, and is probably brought about by many agencies, including chemical organizers, the restraining effect of the periosteum, and the action of the muscles. The young bone at the metaphysis is often more bulky than future requirements demand, and by the process of remodelling it is reduced in quantity and increased in density to attain the requisite thickness and compactness of the shaft. Examples of failure of the remodelling process during skeletal growth are found in the dystrophies now grouped under the title *diaphysial aclasis* (see p. 129).

In adult life the remodelling process effects alterations in the structure of any part of a bone, according to its special needs. An outstanding example of this is seen when the statics of a bone is altered by the union of a fracture in faulty alignment. To meet the altered axis of weight-bearing the bone and callus assume a dense lamellated structure in the new lines of pressure, whereas parts subjected to less stress are relatively porous.

RELATION OF BONE TO THE METABOLISM OF CALCIUM AND PHOSPHORUS

The elements calcium and phosphorus have an important part in many metabolic processes, and are essential for such basic activities as the mechanism of the heart beat, the contractility of muscles, the irritability of nerves, and the regulation of acid-base reactions. The rôle of the skeleton is to act as a storehouse for these elements, and thus to ensure a constant level in the blood, so that it is not surprising that any disease which affects calcium and phosphorus metabolism is reflected in the bones.

Calcium and phosphorus are obtained from the food by absorption in the alimentary tract, and such portions as are not utilized are eliminated in the fæces and urine.

Calcium is absorbable only in soluble form. Its absorption is therefore impaired when there is an excess of phosphates or alkalies in the diet, which leads to precipitation of the calcium, or when fat digestion is incomplete, a condition leading to precipitation of calcium soaps. Vitamin D, in virtue of its rôle in facilitating fat digestion, is also a necessary factor in the absorption of calcium.

Calcium is held in solution in the blood in a concentration far in excess of its ordinary chemical solubility. Part of it is adsorbed on to

the serum proteins. The remainder is in ionic form, and is probably maintained in supersaturated solution by the agency of the parathyroid hormone.

The calcium and phosphate ions in the blood are in chemical equilibrium with the solid calcium phosphate of the bones, and are therefore subject to the laws of ionic dissociation. Consequently, an increase in ionic phosphate in the serum leads to diminution of the serum calcium and to deposition of calcium phosphate in the bones. Conversely, a reduction of the ionic phosphate leads to increase in serum calcium and to mobilization of calcium phosphate from the bones. This latter effect is seen clinically in cases of acidosis, where the buffer phosphate is excreted and consequently decalcification of the skeleton is brought about. It is seen also in hyperparathyroidism, for the effect of an increase of parathormone is to remove phosphate from the blood and thus to cause decalcification.

Calcium metabolism is thus dependent upon a great number of factors; adequate diet, unimpaired fat digestion, sufficiency of vitamin D, maintenance of the hydrogen-ion concentration of the blood, and proper functioning of the parathyroid glands. The internal secretions of the pituitary and thyroid glands also play some part in the process. Thus pituitary disease leads to gigantism and acromegaly, and sometimes marked skeletal decalcification. Thyroid dysfunction causes bone atrophy in exophthalmic goitre and dwarfing in cretinism. Even the sex glands are related in some way to the whole process. Their connexion is not obvious in the human, but in animals it is sometimes of great biological importance. In the stag, for example, the growth and subsequent casting of the antlers is intimately related to the seasonal sex cycles, and, as John Hunter observed, if the animal be castrated its antlers are shed prematurely.

It seems probable that the mineral salts of bone are held in a complex molecule which includes calcium phosphate and carbonate along with magnesium, sodium, potassium, chloride, fluoride and hydroxyl groups.

Robison has shown that the deposition of calcium phosphate from the soluble salts in the tissue fluids is effected through the agency of an enzyme, *phosphatase*. This enzyme has been shown to be present in greatest concentration in tissues in which ossification is actively proceeding. It acts primarily by hydrolysing the soluble phosphoric ester, with liberation of free organic phosphate. If a sufficiency of calcium salts be present, the resulting increase in the concentration of phosphate ions leads in turn to precipitation of the complex calcium carbonate-phosphate molecule. The activity of phosphatase appears to depend upon the hydrogen ion concentration of the blood, and is greatest when the pH is deflected towards the acid side—the condition normally present in growing bones or in healing fractures.

THE RÔLE OF THE PERIOSTEUM

In 1741, Duhamel, a French squire of scientific inclination, making use of the recently discovered method of staining bones *in vivo* by the

oral administration of the dye madder, found that increase in girth of a bone is due to the formation of layer upon layer of bone under the periosteum, just as the increase in diameter of a tree trunk is due to the activity of its cambium layer. On the basis of this experimental observation he formulated the theory of the essential osteogenic function of the periosteum, a theory which ever since has been the subject of controversy.

Ollier, of Lyons, was the great protagonist of Duhamel's theory. In his classical work which appeared in 1867, and which contained many valuable observations on the growth of bone, he claimed that the periosteum of young subjects is capable of osteogenesis even when separated from the bone and buried in muscle, and he showed that in adults also the periosteum continues to exercise this function when stimulated by trauma or by infection.

On the other hand, there is the view, which Macewen has powerfully supported, that the periosteum has no bone-forming property, but is merely a vascular fibrous membrane whose function is to limit bone growth. Macewen, as a result of a series of masterly experiments and observations, came to the following conclusions: (1) That the periosteal flaps described by Ollier were not osteogenic unless spicules of bone adhered to them; (2) that the life, growth, and repair of a bone are not affected by removal of its entire periosteum; and (3) that after subperiosteal resection of the shaft of a bone the new bone is formed, not by the periosteum, but by a dual process of proliferation from the cut bone ends, and (in youth) of compensatory overgrowth of the metaphyses. This last conclusion was suggested by experiments in which the bone ends after partial diaphysectomy were covered by metal caps; after six weeks the defect was filled by new bone, and at this time the caps were found to be approximated, indicating that the new bone was derived not from the periosteum but from what remained of the original diaphysis.

As has been stated already, the "battle of the periosteum" is not yet concluded, although many of the apparent discrepancies have been settled. It has been suggested that the periosteum may best be regarded as a double-layered membrane. The outer layer is thick and fibrous, and its function is one of limiting and vascularizing. The inner or "cambium" layer, which is active only in youth, is a thin layer of delicate connective tissue containing numerous osteoblasts, and its



FIG. 41. Regeneration of bone after partial diaphysectomy. A radiogram taken four months after subperiosteal resection of a part of the tibial diaphysis. Note the thick mass of new bone, already sclerosed, which has grown from the upper fragment. A thin wedge of bone from the lower fragment extends proximally under the periosteum.

function is osteogenic. This cambium layer is more intimately connected with the cortical bone, from which it takes origin, than with the fibrous periosteum, and it may with advantage be termed the *epiosteum* (Hey Groves).

Whatever views are held regarding the function of the periosteum, it is beyond doubt that it takes a very important part in pathological processes affecting bone. The periosteum acts as a capsule or restraining membrane to bone, and a bone cannot alter its shape or exceed its normal limits unless the periosteum be removed, raised, or stripped. What sometimes is called "expansion of bone" suggests that bone is distended by pressure from within, but as bone is a rigid structure such a belief is obviously unacceptable. Expansion of bone is dependent on the periosteum being raised by some agency, such as trauma or temporary or recurrent effusions, and a simultaneous softening and decalcification of the underlying bone.

MECHANISM OF BONE FORMATION AND RESORPTION

Since Goodsir in 1845 first applied the microscope to the study of bone growth, it has been assumed almost universally that bone is a product of the vital activity of specific cells known as *osteoblasts*. These are polygonal cells, with dark-staining protoplasm, which show a tendency to arrange themselves in layers in apposition to the bone trabeculae. In youth the osteoblasts are present in large numbers under the periosteum and at the metaphysis, the two regions where bone formation proceeds most actively. They are present also, in either youth or adult life, at nearly all sites of osteogenesis, physiological or pathological.

Most pathologists prefer to regard the osteoblast as a specific type of mesoblastic cell whose purpose is to provide a matrix (osseine or osteoid tissue) for bone, just as the fibroblast is specialised to produce collagen fibrils. Probably the osteoblasts take no part in the deposition of calcium, which is determined more likely by physico-chemical processes.

Resorption of bone consists essentially in the conversion of the insoluble crystalline calcium phosphate of bone into soluble or colloidal calcium phosphate. It is generally accepted that resorption is effected in part by halisteresis—a physico-chemical process in which the calcium is withdrawn by the agency of the body fluids—and in part by the vital activity of the osteoclast cells. These osteoclast cells are multinucleated giant cells with the characteristics of foreign-body giant cells, and they are present around many sites of physiological or pathological bone resorption. They are variously regarded as phagocytic wandering cells, or as modified osteoblasts.

Leriche and Policard have suggested that bone results from a metaplasia or metamorphosis of primitive mesenchyme, which is brought about by a combination of environmental or physico-chemical factors, rather than by the action of any specifically endowed cells. They point out that bone formation occurs always in young mesen-

chymal tissue sustained in certain physical characteristics, and this tissue they call an ossifiable medium. Bone formation depends first upon the presence of such an ossifiable medium, and, secondly, upon the presence of an adequate supply of readily assimilable calcium. According to this hypothesis ossification depends upon local adjustments of the circulation, and is independent of the action of osteoblasts.

In our opinion the greatest importance of the work of Leriche and Policard lies in the prominence they give to the action of circulatory changes in modifying the behaviour of bone. In general it may be stated that excessive blood supply (hyperæmia) is associated with bone resorption; and conversely diminution in blood supply, other things being equal, with sclerosis. These views regarding the changes induced by alteration of the vascularity of bone serve as a valuable means of interpretation for many pathological phenomena, especially in radiological studies of bone diseases.

HETEROTOPIC OSSIFICATION

The development of bone in tissues remote from the skeleton is a rare but interesting process, the reason for which has provided considerable speculation. Heterotopic ossification has been observed quite frequently in the scar of an old abdominal incision, and it may occur in an old hæmatoma, in the wall of an aneurysm, in tumours, and in many other situations.

Ossification in the perichondrium of calcified costal cartilages is another example of the same phenomenon. It is most common in the upper and more stationary ribs. It usually affects elderly people, but it may occur in young subjects, especially if they suffer from chronic pulmonary disease that leads to fixation of the chest wall. The ossification begins close to the sternum and is first apparent near the surface of the cartilage.

In "*myositis ossificans progressiva*," bone formation of a heterotopic character is found on a large scale. The new bone is preceded by calcification and by a proliferative change in the fibrous connective tissues of the muscle (*see* p. 219).

The bone formation occurs always in relation to fibrous connective tissues and in structures that may be regarded as in a state of functional disuse or death, and it is always preceded by deposition of lime salts, such as is of common occurrence in healed tuberculous nodules in lymph glands, blood vessels, or in scar tissue in many other situations.

In the past, heterotopic ossification was generally attributed to the activity of osteoblasts derived from local or distant sources. Thus, ossification in the abdominal wall was ascribed to injury to the pubis or xiphisternum, with consequent liberation of osteoblasts; whereas ossification in other situations was thought to be due to the action of osteoblasts migrating from the blood stream into the injured tissues.

The present-day view is that the presence of specific cells (osteoblasts) is not essential, and that if the requisite conditions of vascularity and calcium supply are present any primitive mesenchymal cells may assume the osteoblastic function.

UNION IN FRACTURES.

It is customary to describe three stages in the repair of a fractured bone : (1) the stage of blood-clot and granulation tissue, (2) the stage of callus, and (3) the stage of ossification. These divisions, though rather arbitrary, serve to mark the various phases of healing in bone.

Soon after fracture the bone ends and lacerated tissues about them are surrounded and infiltrated by blood-clot, which may vary in amount and in distribution in different fractures. Newly formed capillaries invade the clot, along with phagocytic cells and fibroblasts, which slowly replace the clot by a vascular granulation tissue. If the fracture is examined after about ten days the tissues will be found to be very gelatinous, and a clear, slightly pink jelly covering the ends of the bones will be observed. A little later calcific material is deposited in the exudate, which, at this stage, is sometimes known as the pro-callus.

In the intermediate stage of repair islands of new bone appear in the calcium-infiltrated granulation tissue, and to this mass of newly formed bone and proliferated tissues the name callus is given. The early callus is usually soft and forms a roughly globular or spherical mass between and at the ends of the bones as well as for a variable distance in the surrounding soft parts. The amount of callus and its disposition in relation to the bone ends is very variable and is influenced by many local factors. The portion outside the bone and beneath the true periosteum is known as the external callus ; that which plugs the interior of the bones is the internal callus ; and that connecting the actual fragments is the intermediate callus. When healing is complete only the intermediate callus persists, and throughout life it shows a slightly greater density than the adjacent bone.

The amount of callus which is deposited at the site of fracture is very variable. It depends, among other things, on the site of the fracture and the degree of damage to the bone. Thus it is greater in oblique or comminuted fractures than after simple transverse fractures or after osteotomy. In greenstick fractures the amount of callus tends to be relatively large, probably as a result of hæmorrhage from the vascular periosteum. In fractures of the skull there is little or no callus formation. The amount of callus tends to be increased by movement during the repair of the fracture.

Evidence of bone resorption may be very readily seen in radiograms taken at intervals after fracture. They show decalcification and rarefaction of the bones at the site of fracture and for a variable distance beyond it. The result of such resorption is appreciated if the fracture is exposed at operation, when it is found that after about ten days the bone ends have lost their sharp spiculation, and are more porous and, as a result, less readily adaptable to one another. If looked for, the jelly-like pre-osseous substance may be found on the fragments ; it may be regarded as the primitive callus in which deposition of lime salts is to occur prior to actual bone formation. New bone is rarely apparent until about the tenth day, and twenty-five days usually elapse before the callus becomes firm. Toughening of the callus is probably caused by the gradual return of the local circulatory conditions to normal.

At an early stage of the formation of a mass of callus a thick and oedematous covering of periosteum is found. Later it becomes tough and fibrous and forms an investing membrane at the site of union.

Delayed union or non-union is often met with in the long bones, and there are some sites at which it is especially common. These are the neck of the femur in old subjects, the distal third of the ulna, the distal part of the tibia, the middle of the shaft of the humerus, the patella and the olecranon. Non-union is very common in fracture of the carpal navicular and of the calvaria.

When the fragments of bone are exposed in a case of non-union of long standing their ends are generally found soft, spongy and rarefied. Sometimes absorption has taken place to such an extent that a considerable gap separates the fragments. In some instances, especially those associated with pseudarthrosis, there is sclerosis of the ends of the bones, especially of the distal fragment which may be cup shaped. Sometimes an encysted collection of serous fluid is found within the fibrous capsule uniting the bones.

Non-union may be attributable to constitutional or local causes. Constitutional predisposing causes are not well defined. It is generally stated that severe anæmia, wasting diseases, syphilis, diabetes mellitus and chronic renal disease predispose to non-union, but it seems probable that their importance has been over-estimated.

Local predisposing causes of non-union are of three main varieties : (1) mechanical hindrance to the approximation of the fragments and their union by callus, (2) interference with the normal biological process of new bone formation, and (3) inadequate immobilization. Sometimes the factors are combined.

(1) Mechanical hindrance to the approximation of the fragments may result from wide separation of the fragments or from interposition of soft tissues such as muscle and fascia. Actual new bone formation may be attempted, and the bone may invade the interposed muscle, but it is deposited in the axis of the muscle fibres and lies at right angles to the fragments, and is thus of no value in cementing the fracture.

(2) Interference with the normal biological process may result from infection, pre-existing disease in the bone, derangements of the local circulation (as by rupture of a nutrient artery), and other factors.

Infection is an important cause of non-union and accounts for the frequency of this complication in compound fractures. The presence of a foreign body may further militate against repair. Infection may disturb the processes of union in several ways : (a) by causing necrosis of the fragments, (b) by causing destruction of the young bone-forming elements, (c) by delaying the normal process of new bone production to such a period that some of the essential factors for osteogenesis are lost. Such is the part played by fairly severe infection, but in the presence of a mild degree of infection, union is often very firm and attended by an excess of callus.

Pre-existing disease of bone such as cysts, tumours, or osteomyelitis may determine non-union, but it is remarkable that not infrequently union may occur even in the presence of extensive local disease.

(3) In the repair of some fractures a slight degree of movement is

regarded as beneficial, and many surgeons encourage active movement of a fractured bone from the onset of treatment. None the less, there are many sites at which this practice must be regarded as injurious and likely to promote non-union. Many indeed believe that the most fruitful source of non-union is faulty immobilization, especially such as permits of repeated slight shearing or torsional strain at the bone ends; and it is significant that those fractures which fail to unite are precisely those which are difficult to immobilize completely. Experience in the management of common fractures such as that of the carpal navicular and the femoral neck in old subjects has afforded convincing evidence of the importance of securing firm fixation of the fragments and protection of the developing callus. In intracapsular non-impacted fracture of the neck of the femur non-union is almost invariable unless immobilization is obtained. Following immobilization, secured preferably by operative means, firm union results in a considerable number of cases. Non-union at the neck of the femur is associated usually with marked absorption of bone locally and cupping of the distal fragment, which, formerly, was attributed to atrophy as a result of rupture of the nutrient vessels; but, more likely, the disappearance of bone and the non-union are due to disturbance of the callus induced by the trauma of recurring slight movement, or to aseptic necrosis of the proximal fragment.

In fracture of the carpal navicular, union is uncertain unless movement of the wrist and carpal joints is abolished during treatment. The non-union resulting from too early resumption of movement can generally be overcome by prolonged immobilization.

In some situations it appears that excessive mechanical traction may be responsible for delayed union as a result of undue separation of the bone ends.

TRANSPLANTATION OF BONE

Bone transplants are commonly employed in orthopædic and plastic surgery. They are required most frequently to restore continuity and to promote union of a fractured bone. Sometimes they are used to bridge the gap resulting from injury, necrosis or operative interference. In other instances they are of service to immobilize a tuberculous vertebra, to deepen the acetabulum in congenital dislocation of the hip, or to stabilize a flail joint.

The transplant may consist of living or of dead bone. Living bone may be derived from the same subject (*autoplastic*), or from another individual of the same species (*homoplastic*). Dead bone is usually derived from another species, and is conveniently obtained from beef bone that has been boiled and suitably shaped. Occasionally, portions of ivory in the form of pegs or nails are employed.

Autoplastic transplants are most generally useful. They may be derived from near the site of intended implantation, for example, the bone adjoining a fracture, or from some other part of the skeleton, such as the subcutaneous surface of the tibia, the proximal end of the fibula, or one of the ribs. A single large transplant or a number of small fragments, "bone chips", may be used. Custom, circumstance and

ingenuity play a prominent part in determining the site for obtaining the transplant, and the ease with which a transplant may be taken from the tibia makes this the favourite source. The ribs, though accessible and of suitable curvature for many purposes (e.g., repair of defects in the skull), do not provide satisfactory transplants on account of their lack of substantial cortex.

The Fate of Bone Transplants. This is a problem on which there is no general agreement. Transplants of dead bone (such as beef bone or ivory) are generally believed to subserve two principal functions: (1) to give stability at the site of implantation, and (2) to act as osteo-conductive agents, scaffoldings along which new bone may be deposited. The dead transplant acts as a foreign body and stimulates a reaction on the part of the surrounding tissues.

Transplants of living bone give stability and act as osteo-conductive agents, and in addition, it is believed, they encourage osteogenesis. It is believed that they serve this purpose best when transplanted with the periosteum retained.

The viability of a living transplant is a subject of controversy. The view most widely held is that a thin superficial layer of the transplant survives, the cells of this part acquiring nourishment from tissue fluids and effused blood serum. The remainder of the transplant dies and then functions as a dead transplant. If the transplant be examined forty to sixty days after its implantation it will be found to be rarefied, and the Haversian canals are wider than normal, and are invaded by granulation tissue and newly formed blood vessels.

Radiological studies show that in most cases the transplanted bone is gradually absorbed, and simultaneously new bone is formed in the tissues around it. It must be noted, however, that in some bone transplants, notably pegs inserted into the marrow cavity and transplants used for spinal fixation, the shadow of the transplant is visible for many years. In such cases it must be conceded that the transplant either has lived unchanged, or after serving its purpose has become incorporated in the tissues as a foreign body.

OSTEOMYELITIS

Any inflammatory process involving bone and marrow may be called osteomyelitis, but the unqualified term is generally restricted to non-tuberculous lesions due to pyogenic micro-organisms. The disease may follow direct infection from local sources, as in compound fractures or from an open wound, or it may result from hæmatogenous infection derived from distant sources. The hæmatogenous type will be described first. It is principally a disease of childhood or of adolescence, and when it does affect adults the pathological process is somewhat modified.

ACUTE OSTEOMYELITIS

This is a common disease, and a grave and often fatal one. Boys are affected three times more frequently than girls, and most often between the ages of three and ten years.

In the great majority of cases the infecting organism is the *staphylococcus aureus*. The *staphylococcus albus* or streptococci are sometimes the causal agents, and occasionally in young children pneumococci. The origin of the infection is not always obvious. Sometimes a boil or septic abrasion in the skin is present, sometimes the tonsils are inflamed, but very frequently it is impossible to detect a primary focus.



FIG. 42. Septic osteomyelitis of the tibia, of three and a half years' duration, in a man aged twenty years. There is a massive involucrum perforated by numerous cloacæ, through which a large sequestrum may be seen.

(Museum of Royal College of Surgeons of Edinburgh.)

In most cases the disease appears to start as a septicæmia. The circulating organisms then settle in favourable situations in the bones and there lead to an acute suppurative inflammation. Often there is a history of a recent minor injury to the affected bone, and probably a small traumatic hæmorrhage forms the nidus favourable to the growth of the infecting organism.

The septicæmic phase may be of short duration, or it may be prolonged during several days. In the latter event multiple foci may develop in several bones, simultaneously or in succession—a feature which suggests that the organisms may have some specific affinity for osseous tissue. In severe cases the septicæmia continues, finally giving place to pyæmia.

The Local Lesion. The bone focus is generally situated in the metaphysis, which is the region of most active growth and consists of young vascular bone, easily traumatized.

At the onset of the bone lesion there is an outpouring of leucocytes around the organisms, and an abscess containing thick yellow pus rapidly forms. Around the abscess

there is a zone of intense hyperæmia. The infection then spreads (1) to the surface, causing subperiosteal effusion, (2) down the medullary canal, and (3) rarely through the epiphysis. The infection traverses the Haversian and Volkmann's canals in the cortex, and erupts under the periosteum, raising it off the bone surface. Since the periosteum is closely attached to the circumference at the epiphysial cartilage the infection does not spread towards the joint except in certain regions, such as the hip, where the metaphysis is intra-articular. When the periosteum is elevated from a wide area the small periosteal arteries

become obliterated, and the blood supply to the cortex is impaired. Superficial portions of the bone undergo necrosis and may later form sequestra. Rarely the principal nutrient artery to the bone may be occluded by thrombosis, and then the greater part of the diaphysis dies.

At operation in the early stages the bone does not bleed, the vessels of the marrow are occluded by blood clot, and bily droplets escape from the wound. Later, the periosteum over the affected bone is thickened and very congested. It is raised off the bone, and when it is incised there escapes a quantity of thin yellow pus. Sometimes, if the original focus lies beneath the cortex, this outlet suffices, but often it is advisable also to explore the bone in the region of the metaphysis to evacuate pus confined within the cancellous bone.

Necrosis of bone is usually greatest in the region of the metaphysis, where thrombosis and toxic inflammatory products pent up under tension destroy the living framework of the bone. In this region the whole thickness of the bone, or its greater part, may become necrotic. If the periosteum has been widely elevated there may also occur necrosis of the superficial parts of the denuded cortex. When the whole marrow has been invaded, the greater part, or even the whole, of the diaphysis may die. Fortunately, however, this extensive necrosis is much less frequent than examination of museum specimens suggests.

The dead portion of bone is at first continuous with the living, but demarcation is not long delayed; its surface, denuded of periosteum, is smooth and shiny and white; when percussed it emits a "dead" sound; and when pierced by an instrument it does not bleed.

Around the margins of the dead bone there rapidly develops a foreign-body reaction, and small portions of necrotic bone may be completely absorbed, but large ones remain until extruded or removed by operation. Around the dead mass, in the interstices of the adjacent living bone and in such of the periosteum as is in contact with the bone, there develops a vascular granulation tissue, which erodes the bony trabeculae and eventually sets the dead mass free as a sequestrum. In the process of separation the sequestrum loses much of its calcium, and where the granulation tissue has been in contact with it, there is an eroded, worm-eaten appearance. The surface denuded of periosteum and bathed in pus is not subject to this erosive process and, for a long time, remains smooth and shiny.

FIG. 43. Osteomyelitis of the tibia. Almost the whole diaphysis has undergone necrosis, and is seen as a smooth, shiny sequestrum, surrounded by a rough, irregular involucrum.

(Museum of Royal College of Surgeons of Edinburgh.)

The sequestrum, when completely loosened from its attachments, lies in a cavity in the bone, and interferes with healing, often for years. In rare instances it may be extruded from a sinus; usually it remains encased within the involucrum.

New bone formation may be regarded as a reactive and reparative process, although its effects are not invariably beneficent. The new bone forms both on the surface and in the depths of the old, so that outside the actual area of destruction the bone becomes increased both in girth and in density. The new bone is formed in greatest amount immediately deep to the periosteum, and when this membrane has been widely elevated an extensive new case of subperiosteal bone—an *involucrum*—may develop. At first the involucrum is porous and light, but gradually it becomes more calcified, and in the course of years it may become sclerosed. Its surface is always rough and irregular, and it is usually perforated in one or more places by *cloacæ*, circular everted apertures that mark the position of sinuses, or of gaps where purulent discharge has prevented regeneration of bone.

Infection of a neighbouring joint is fortunately an uncommon complication, although a sterile "sympathetic" effusion of clear or of turbid fluid, due to hyperæmia of the synovial capsule, is not unusual. Until ossification is complete, the epiphysial cartilage, on account of its avascularity, offers a secure barrier against joint infection *viâ* the bone, and the attachment of the periosteum to the circumference of the cartilage limits subperiosteal spread in that direction. Where part of the metaphysis lies within the articular capsule, however, as at the hip, the joint is affected more readily, for as soon as infection reaches the surface of the bone it erupts through the synovial capsule. In infancy the young vascular cartilage which forms the greater part of an epiphysis offers little resistance to infection, and consequently osteomyelitis at this early age is very apt to be complicated by infection of the joint—*acute arthritis of infants*.

Constitutional Effects of the Disease. The general effects of acute osteomyelitis are usually severe, for the pent-up inflammatory products discharge highly toxic substances into the blood stream. There is high fever, with great constitutional disturbance. Pyæmia may supervene, as a result of dissemination of infected thrombi from the large veins of the narrow spaces. Lung abscesses, pericarditis endocarditis and abscesses in the kidneys or spleen may result. Formerly, due to neglect, continued suppuration led to amyloid disease.

Acute Osteomyelitis in Adults

Osteomyelitis is much less common in adults than in children, and, since the general resistance to staphylococcal infection seems to be raised, the disease is neither so rapid in progress nor so uniform in character. In adults there is no metaphysis, and such local predisposing factors as result from the rapid growth of bone are absent. Consequently, any part of a bone may be affected. Trauma often seems to be a definite predisposing factor, and such exposed regions as the medial surface of the tibia are likely to be affected. The course of the disease is slow and the symptoms are less severe.

Acute Osteomyelitis in Special Situations

It is noteworthy that the more peripheral the bone affected the less severe is the disease. The site most commonly affected, the proximal end of the tibial diaphysis, is fortunately one of the least dangerous, and the superficial position of the bone facilitates early recognition of the disease. When the upper end of the femur is attacked constitutional features are usually pronounced, and in early childhood the hip joint is often involved. At the distal part of the femur the loose attachment of the periosteum on the underlying cancellous bone favours early abscess formation in the popliteal fossa, and from deprivation of blood supply to the bone massive sequestration is a common feature.

Osteomyelitis of the vertebrae is a rare disease, but one of great gravity. Adults are affected more often than children. If the infection arises in a spinous process or lamina the pus may make its way to the surface and do little damage, but if the vertebral body is diseased a fatal outcome is likely. The deep situation, the lack of localizing symptoms, and the great constitutional disturbance combine to obscure the diagnosis; complications from spread of infection to vital structures rapidly supervene; and surgical approach for the purpose of drainage is very difficult.

In the cervical region an abscess which develops in the prevertebral space may pass to the mediastinum; in the thoracic region mediastinal cellulitis and empyema commonly occur; and in the lumbar region a rapidly extending psoas or an acute perinephric abscess may form. Finally, the infection may pass towards the spinal canal and give rise to spinal meningitis.

Osteomyelitis of the pelvic bones is a serious disease and the profound constitutional disturbance usually overshadows the local features of the infection. Any of the bones may be affected, usually in relation to one of the many epiphysal cartilages, especially the pubo-ischial. From the ilium an abscess may develop on the pelvic aspect or superficially under cover of the gluteal muscles. From the pubis the abscess may rupture into the bladder, and a sequestrum may even perforate it.

CHRONIC OSTEOMYELITIS

Chronic osteomyelitis is usually a legacy of the acute disease, but it may arise insidiously and pursue a slow course.

In the type that succeeds the acute disease there are usually one or more sinuses communicating with the exterior. The surface of the bone is very irregular, either over its whole extent or over one end of the shaft, and it is thickened by new subperiosteal bone. At the metaphysis, or extending for a variable distance within the bone, there is an abscess cavity, sometimes of considerable dimensions. Around the cavity the bone becomes greatly increased in density, and the neighbouring marrow cavity is obliterated by new bone formation. Sometimes there are several small cavities within the sclerotic bone.

Apart from lingering or relapsing infection the principal factors that prevent healing and maintain the disease in its chronic state are the rigidity of the wall of the bone cavity, and/or the presence of one or more

sequestra within it. Small sequestra may be discharged at intervals through sinuses, and sometimes small fragments of bone migrate to the surface many years after the original infection, even after healing of the skin. Massive sequestra are usually entrapped within the involucrum and until liberated constitute a source of continued suppuration..

The insidious form of chronic osteomyelitis, due to staphylococcal infection, is somewhat rare. It usually affects adults. Scanty or avirulent organisms carried by the blood stream are deposited, usually at the metaphysis, and here give rise to a low-grade inflammatory reaction. The so-called *Brodie's abscess* commonly results. This is an abscess in the bone, most commonly in the proximal end of the tibia, less often in the distal end or in the femur or the humerus, or more rarely elsewhere. The cavity lies in the central axis of the bone and is at first close to the metaphysis, but may be removed from it as the bone grows. The abscess is usually of small size, a centimetre or less in diameter, buried in sclerosed bone. Overlying it, the surface of the bone is often irregular from new subperiosteal proliferation. The abscess sometimes remains for years with little sign of activity, and in these circumstances it often contains sterile gelatinous granulations and is surrounded by a fibrous wall. No sequestrum is present as a rule. With more active infection the abscess may enlarge and become filled with thick pus, from which organisms may be cultivated.

A Brodie's abscess may remain unrecognized for a long time; occasionally for many years. Pain of a dull aching or boring nature is felt in the bone, especially at night, and the neighbouring joint may be the seat of recurring effusion. A striking feature is the great sensitiveness of the bone overlying the abscess. A radiogram displays the cavity surrounded by dense bone.

Chronic Hypertrophic Osteomyelitis. Osteomyelitis may be chronic from the onset and may then result in extensive hypertrophic changes in the affected part, usually one of the long bones. The infecting organism is usually the staphylococcus aureus. The disease tends to affect young adults, but sometimes it occurs in later life. The commonest sites for this somewhat rare type of osteomyelitis are the lower end of the femur, the upper end of the humerus, and the tibia. It has been observed also in the clavicle and in the radius.

When seen at operation the affected part of the diaphysis shows a fusiform thickening due to the deposition of new lamellæ of bone beneath the periosteum. The periosteum and bone at the affected area are abnormally vascular, and the marrow cavity may be obliterated. Generally there is no suppuration nor sequestrum formation, but occasionally a small abscess is encountered. The infecting organism can usually be cultivated from excised bone chips.

The condition is associated with aching pain and slight swelling of the affected limb, and movements of the neighbouring joint are often restricted and painful. Intermittent slight rises of temperature are often noted, and examination of the blood shows a slight polymorphonuclear leucoeytosis, seldom higher than 14,000 cells per c.mm.

The importance of this form of osteomyelitis is its resemblance to

sarcoma, and very careful and repeated radiological examinations or even biopsy may be required to establish its nature.

Pneumococcal Osteomyelitis

This form of osteomyelitis is not uncommon in young children. In 200 cases of osteomyelitis reported by Fraser, the pneumococcus was responsible for 29%. The disease generally runs a mild course, and causes but slight increase of temperature and few constitutional symptoms. The pathological features resemble those of staphylococcal osteomyelitis, except that in place of thick pus there is a turbid watery exudate. A similar lesion is sometimes produced by staphylococcus albus, and from the watery nature of the effusion it is sometimes known as *serous osteomyelitis*.

Typhoid Osteomyelitis

In the septicæmic stage of typhoid fever the bacilli appear to find the bone marrow a favourable nidus, and it has been shown that they may be cultivated from this tissue almost as frequently as from the spleen. Moreover, they may remain latent in the marrow long after the original disease has subsided, yet cause no symptom until awakened to activity, perhaps by some mild trauma or other disposing factor.

Typhoid osteomyelitis arises usually from four to six weeks after the onset of the fever, but it may appear months or even years later. The ribs are affected most often, especially in the neighbourhood of the costo-chondral junctions, and the cartilage close by may also be affected. In other cases the sternum, the bones of the pelvis and the spine, the ulna or the tibia may be involved. The disease takes a mild course, either insidious in progress or with recurring mild exacerbations, and there is usually little new bone formation, and only slight tendency to the formation of sequestra. Sometimes the bacilla are present in pure culture, and the pus is then scanty and rust coloured from altered blood. More often there is mixed infection with *B. coli* or *staphylococci*, and the pus is then of the type characteristic of these organisms.

Osteomyelitis Following Local Infection

Any open wound communicating with a bone, a compound fracture, burn, or an abscess in the neighbourhood of a bone, is apt to lead to some degree of osteomyelitis. The extent and severity of the infection vary in different cases, depending partly upon the nature and virulence of the infecting organisms, and partly upon such other factors as the amount of damage to the soft parts and the amount of foreign material introduced. The severest lesions are those associated with much devitalization of the bone or soft tissues, as in gunshot wounds and street accidents, and if a virulent infection is introduced the whole bone may undergo necrosis. Minor injuries with slight infection may lead merely to superficial inflammation (periostitis), or perhaps to necrosis of small flakes of cortical bone.

A classical example is *osteomyelitis of an amputation stump*, and in what may be called the amputation era of surgery many specimens of



this affection found their way into museums. The open medullary canal formed a ready route of entry for organisms, and these were spread widely along the bone or remained near its extremity. In the latter case a sequestrum usually resulted, which involved a short annular portion of the cortex, often with a longer tapering portion of cancellous bone.

Bone Changes resulting from Adjacent Inflammation

The bones adjacent to an acute inflammatory process may share in the regional hyperæmia and undergo considerable osteoporosis which, in some situations, may lead to grave effects. One of the most notable examples of this process has been observed in the upper cervical vertebræ in association with acute inflammatory lesions of the pharynx and of the glands of the neck. The hyperæmic decalcification of the vertebræ, particularly of the atlas and axis, may allow of loosening or separation of the intervertebral ligaments resulting in forward luxation or dislocation of the atlas. The displacement may occur spontaneously or from trivial violence. It may occur without complications, but in some cases it has led to compression of the cord giving rise to quadriplegia; in others the compression has been fatal.

When the local inflammatory process is less acute, as for example in a chronic ulcer of the leg, the reaction in the underlying bones is quite different. The inflammatory hyperæmia, which may vary in intensity from time to time, leads to a proliferative reaction in the periosteum and effusion beneath it. New bone formation occurs irregularly as osteophytic outgrowths beneath the periosteum and in the interosseous membrane (Fig. 44), and its form and distribution may be modified by gravity or by muscular action.

FIG. 44. A macerated specimen of the distal two-thirds of the left tibia and fibula, illustrating the development of osteophytes which commonly occurs in a case of chronic leg ulcer. The new bone formation is most abundant at sites of muscular attachment and in the plane of the interosseous membrane.

(Museum of Royal College of Surgeons of Edinburgh.)

SYPHILIS OF BONES

The bones may be affected in both the second-

ary and tertiary stages of acquired syphilis or in inherited syphilis. Nowadays the disease is seldom seen.

In general, the pathology is fundamentally the same as that of syphilis in other tissues, but modified by the special anatomical and physiological attributes of the bone. Spirochaetes carried in the blood are deposited in the bone and lead to a cellular reaction. There is an infiltration of the periosteum by endothelial cells and lymphocytes, granulation tissue is formed, and subsequently this leads to fibrosis. Sooner or later, as in all syphilitic manifestations, there is a considerable degree of endarteritis obliterans around the affected parts. The bone at the site of the lesion may undergo temporary decalcification and partial destruction, but later when the vascularity of the part diminishes it is apt to become sclerosed.

The bones most liable to syphilitic lesions are the tibia, sternum, ulna, clavicle, and the bones of the calvarium. In the long bones the lesions are situated usually in the diaphyses, and consequently syphilis of the bones, unlike tuberculosis, rarely leads to joint involvement.

Secondary Stage. In the secondary stage of acquired syphilis the bones are liable to be involved after the period of the skin eruptions. The tibia is affected most often. Commonly there is a periostitis, which is mild and transient. The periosteum is infiltrated with round cells, and becomes painful and tender to pressure. In some cases multiple areas of fibrous tissue develop—*periosteal nodes*—which, in superficially placed bones like the tibia, may be obvious as localised tender swellings.

Tertiary Stage. In the tertiary stage of acquired syphilis the bones may be affected either by localized gummata (single or multiple) or by a diffuse gummatous osteo-periostitis.

Gummata affect the tibia often, and are situated generally at the proximal third of the diaphysis. The sternum also is affected frequently. Less often gummata occur in the ulna, the clavicle, or the bones of the skull. The first stage in the formation of a gumma consists in a cellular infiltration of the periosteum. Later there is a proliferation of granulation tissue, which decalcifies the subjacent bone, often in a serpiginous manner. Subsequently the tissue becomes fibrous, and forms a firm mass raised above the surface of the bone. Multiple gummata may fuse and form a swelling of large size which may simulate a new growth.

As the granulation tissue, loaded with calcium from destruction of subjacent bone, undergoes fibrosis, it provides a medium suitable for ossification. The new bone formed in it gives rise to a rough irregular eminence on the surface of the shaft, a so-called *hard node*. As a result of the ischaemia induced by endarteritis obliterans the bone in the vicinity of the gumma commonly undergoes extensive sclerosis.

Sometimes the gumma softens in the centre and breaks down to form an abscess or ulcer of characteristic appearance, with an indurated, sharply defined, "punched-out" margin and a yellowish sloughing base. The ulcer provides an avenue for superadded infection, and a septic osteomyelitis may then develop, which may result in necrosis of the bone and sequestrum-formation. Eventually an ulcerated gumma may heal, leaving a glazed, yellow-coloured scar. Gummatous

ulcers develop most often in relation to the bones of the skull, and super-added infection may then lead to suppuration inside the cranium.

Diffuse gummatous osteo-periostitis results from an infiltration similar to the localized infiltration of a gumma. The diaphysis of the tibia is affected frequently. The bone eventually undergoes sclerosis, and much new bone of dense structure is formed, both on the surface of the shaft and within its marrow cavity. The bone is greatly increased in weight. The periosteum is thickened, and adheres firmly to the surface of the bone, which is rough and irregular. The marrow cavity is encroached upon and may be totally obliterated.

Inherited Syphilis.

Some of the bone lesions of inherited syphilis may be congenital, whereas others develop during childhood and adolescence.

Syphilitic osteochondritis or epiphysitis is one of the commonest of the early lesions. It occurs usually during the first six months of life, and it affects especially the lower end of the femur, but also the tibia, the fibula, or the bones of the forearm. Often the affection is multiple and bilateral. Being painful, the lesions prevent free movement, and the limbs may appear to be paralysed (pseudo-paralysis of infancy). The pathological process consists of an infiltration of the metaphysial regions of the bones by

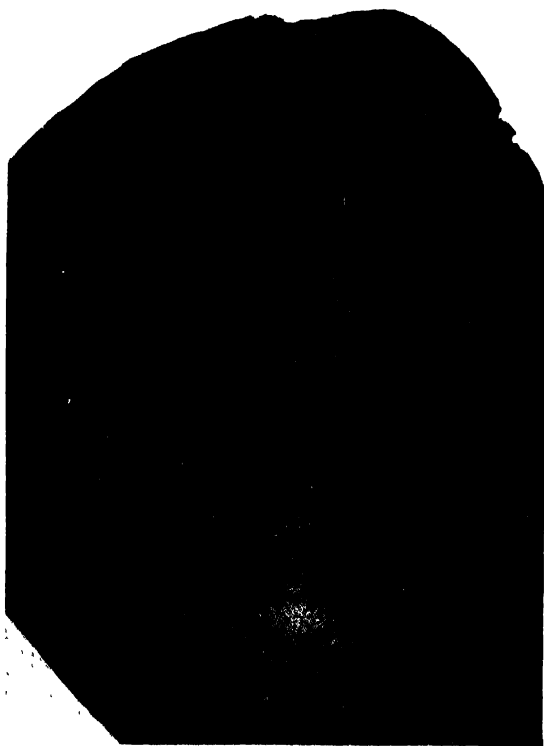


FIG. 45. Syphilitic osteitis of left parietal bone, from a child aged two and a half years.

(Museum of Royal College of Surgeons of Edinburgh.)

lymphocytes and granulation tissue. Ossification of the metaphysis is interrupted, and the bone already present undergoes decalcification.

When the affected area is cut across it is seen that the thin transverse line that normally marks the zone of new bone formation is replaced by a broad irregular band of a yellowish colour, and in this region the bone is softer than usual. The cartilage becomes softened, and separation of the epiphysis may occur. Effusion in the neighbouring joint is not uncommon.

Gummata, and *diffuse gummatous osteoperiostitis* may occur in

inherited syphilis. They have the same characters as in acquired syphilis, and tend to affect the same bones, especially the tibia and sternum. The tibia is liable especially to a diffuse osteoperiostitis, and as a result it becomes greatly thickened and sclerosed. Usually it becomes curved, with the convexity anteriorly, and is flattened from side to side, the so-called sabre tibia. Sometimes the sharpness of its margin is obscured and the bone may then resemble a cucumber in shape.

Syphilitic dactylitis is a form of osteoperiostitis affecting the metacarpals, metatarsals, or phalanges. The proximal phalanx of the index finger or thumb is most liable to the disease. New bone is formed under the periosteum, and a cylindrical, sclerotic enlargement results. Growth of the bone is interfered with and the digit may remain permanently short.

The cranial lesions of inherited syphilis are now recognized to be attributable to the malnutrition and debility associated with the disease more often than to a specific infection of the bone. Thus craniotabes, a condition of decalcification and thinning of the flat bones, particularly the occipital bone, is the result of malnutrition and is comparable to the cranial atrophy seen in rickets. "Parrot's nodes," the large bosses of spongy bone that form in the region of the frontal and parietal tuberosities, also have their counterparts in rickets. Erosions of the bones of the palate and nose, which result in perforations of the palate and in the characteristic depressed, saddle-shaped nasal ridge, are secondary results of combined septic and syphilitic lesions of the mucous membranes.

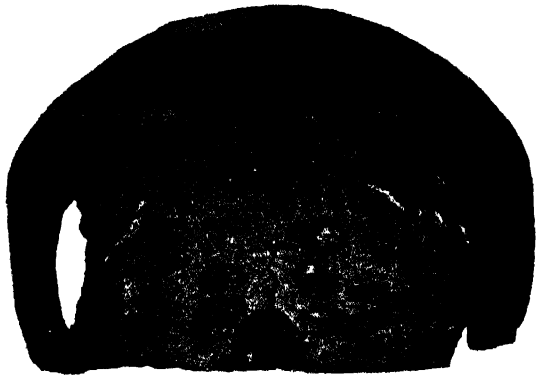


FIG. 46. Syphilitic osteitis of the frontal bone, from a child affected by inherited syphilis. The diploë and outer table are extensively destroyed, and in places the inner table is perforated. The ulcerative process is irregular in distribution, and gives a worm-eaten appearance.

(Museum of Royal College of Surgeons of Edinburgh.)

DIAPHYSIAL ACLASIS (Multiple Exostoses)

The term diaphysial aclasis has been applied by Keith to certain diseases characterized by disturbance of the growing ends of bones. The most notable example is the condition formerly known as *multiple exostoses*, but there is much evidence that the rarer *dyschondroplasia* should be included, as well as, perhaps, such conditions as *solitary exostoses* and *multiple chondromata*, which are usually classed as benign tumours.

Diaphysial aclasis usually occurs as a hereditary disease, and sometimes three or four generations are affected. The lesions are not recognizable at birth but appear in childhood. They are rarely very noticeable before the eighth or tenth year. Males are affected three times more commonly than females.

The disease is characterized by three associated pathological features, but all are not present in every case. The three features are: (1) multiple irregular outgrowths of cartilage and bone, (2) failure of bone modelling at the ends of the diaphysis, (3) deficient growth in length of the long bones.



FIG. 47. Diaphysial aclasis. Posterior aspect of the right knee joint, showing multiple exostoses arising from the metaphyses.

(Museum of Royal College of Surgeons of Edinburgh.)

(1) The irregular outgrowths or exostoses constitute the most obvious feature of the disease. They are multiple and often in large numbers. They occur most frequently near the distal metaphysis of the femur and the proximal metaphysis of the tibia, but they may affect the humerus and other long bones, the scapula, the members of the pelvic girdle, and occasionally any other bone formed in cartilage. Exostoses of this type never arise from bones formed in membrane, and they never arise from epiphyses.

The exostoses are composed of unmodelled bone. Sometimes they are conical or pointed, sometimes rounded and globular. As a result of continued growth in length of the bone affected, the conical exostoses tend to point obliquely, away from the neighbouring epiphysis. Often one such conical projection lies at the junction of the normal and abnormal parts of the bone, whereas the globular projections usually are closer to the epiphysial cartilage. An interesting feature of the disease is that the affected portion of bone is covered with a thin layer of cartilage from which growth proceeds. Ossification proceeds in this cartilage, and thus the exostoses and surface irregularities are formed. At about the age of twenty to twenty-five, when

growth normally ceases, the cartilage ceases to form bone and becomes calcified. Not infrequently excessive growth of the cartilage leads to the formation of multiple chondromata, which are most common in the hands, but may occur in many other situations.

(2) The failure of bone modelling when present is seen at the ends of the diaphyses, and in these regions the bone is deficient in calcium and irregular in structure. Sometimes large rounded islands of cartilage

persist in the bones and are visible in radiograms as clear spaces in the bone shadow. The epiphyses are usually unaffected, but occasionally they are small, of irregular outline, and prematurely ossified.

(8) Deficient growth in length is a common accompaniment of diaphysal aclasis. The subjects of this disease are usually of less than average height, from premature cessation of growth of the long bones, and sometimes they are actually dwarfed. In some cases the paired bones in the forearm and leg grow unequally and this leads to deformities.

The Nature of the Disease. The precise limitation of the lesions to the metaphyses of bones formed in cartilage indicates clearly that the fundamental feature of the disease is a disturbance of endochondral ossification, and that the disturbance does not occur in the early embryo but begins after the major portions of the bones have been normally formed. According to Keith, the essential factor is a failure of bone-modelling, the process whereby normally bone newly formed at the metaphysis is remoulded and adapted to become a part of the shaft. The bone formed after the onset of the disease consequently remains unmodelled, with scanty Haversian systems irregularly disposed, and sometimes interspersed with masses of unaltered cartilage. The layer of cartilage on the surface, from whose deep aspect the growth of the exostoses proceeds, is believed to be derived from the epiphysal cartilage.

DYSCHONDROPLASIA (Chondrodysplasia)

Dyschondroplasia was described by Ollier in 1898 as a disease characterized by irregular ossification of long bones and by unilateral dwarfing. The term is now applied also to bilateral affections of similar character.

The disease may affect one bone, one limb, or nearly every bone in the body. It generally becomes manifest in early childhood. The pathological changes are most marked in the metaphysal regions and do not affect the mid parts of the diaphyses. The bone may be somewhat broadened, and is occupied by masses of cartilage, which are traversed and divided by long trabeculae. Exostoses may be present, and multiple chondromata of the hands and feet have been observed.

The disease is now generally regarded as a variety of diaphysal aclasis, but differs from it in that a familial history is often lacking.

FRAGILITY OF BONES

A bone owes its capacity for resisting stresses and strains to two inherent qualities, hardness and elasticity. Hardness of bone is obviously due to the mineral content, whereas elasticity depends upon the soft-tissue elements, the periosteum, the endosteum, the bone cells and fibres. Decalcification of bone leads to softening and pliability, whereas fragility or brittleness is due to affections of the connective-tissue framework and may even occur when the mineral content remains normal. The bones may become fragile in rickets, in infantile scurvy, or as a result of erosion by tumours, but the term "*fragility of bones*"

is usually restricted to certain congenital or inherited diseases of which fragility forms the predominating characteristic.

Fragility of bone may be present in foetal life, or may become manifest in childhood, and for convenience of description it is preferable to recognize two distinct types, *osteogenesis imperfecta*, in which the fragility is evident at birth or in infancy, and "*familial fragility with blue scleræ*," which appears in later childhood.

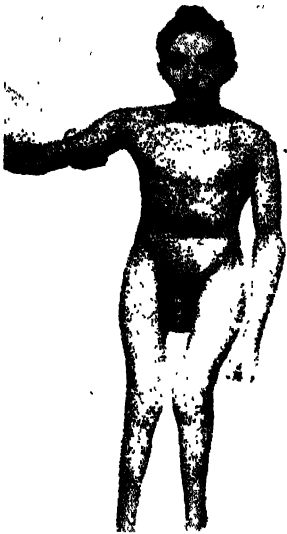


FIG. 48. Familial fragility of bone. The man, aged 21 years, is dwarfed, and shows the characteristic deformity of the head. The femora are deformed, the result of old fractures, and a marked degree of coxa vara is present. Blueness of the scleræ was present, but not marked.

Osteogenesis Imperfecta. The subjects of this disease are usually still-born, but occasionally they survive and may attain adult life. The bones are excessively brittle, and break under the least strain, or even as a result of muscular action. Fractures are sometimes present at birth, and during infancy as many as a hundred may occur, and cause much deformity and shortening of the limbs. Union of the fractures is usually rapid, and sometimes is accompanied by excessive formation of callus. Apart from being fragile the bones may show little departure from normal. They are well calcified, though usually of slender build. Microscopically, there is sometimes evidence of a deficiency in the connective tissue cells of the bone, with irregularity in the disposition of the bone lamellæ.

The long bones of the extremities are particularly liable to fracture, but no bone is exempt. The cranium often presents a curious deformity. It is of relatively large size, and very broad across the temporal regions. Sometimes there is an angular projection above the level of the zygoma, and the upper parts of the auricles may be projected laterally and thus rendered un-

duly prominent. Infants affected with *osteogenesis imperfecta* are usually born of normal parents and there is rarely evidence of an hereditary tendency. Death usually occurs at an early age from intercurrent disease, but if adolescence is reached the liability to fractures diminishes.

Familial Fragility. This is an hereditary disease, which is transmitted in accordance with Mendelian laws as a dominant characteristic. It affects both sexes, and never "skips" a generation.

The fragility is usually, though not invariably, accompanied by other affections, of which the most obvious are blueness of the scleræ, abnormal laxity of ligaments, and a tendency to early deafness. According to Voorhoeve, all these affections are manifestations of an underlying hereditary hypoplasia of the mesenchyme.

Fractures do not usually occur before the second or third year.

They do not occur so readily as in *osteogenesis imperfecta*, nor are they so numerous, and in most cases not more than six or eight occur. The fractures heal readily with well-calcified callus. Fractures are rare after the age of sixteen or seventeen years. At this time the bones tend to become sclerosed, and in a few cases this process proceeds to an abnormal degree.

Blueness of the scleræ usually accompanies familial bone fragility, but is not limited to that disease. The colour varies in depth from a dark greyish blue to "china blue," and it is most evident immediately outside the cornea. It is due to abnormal translucency of the sclera, which allows the pigment of the subjacent uvea and veins to show through. Abnormal laxity of ligaments is sometimes present and predisposes to sprains and dislocations. Lastly, many of the subjects of this disease are liable to otosclerosis, which comes on in early adult life and is steadily progressive.

OSTEOPETROSIS (Marble Bones. Albers-Schönberg Disease)

This rare disease, which may be familial, affects one or more bones, and is most commonly seen at the base of the skull, in one of the vertebral bodies, or in a long bone. The affected bone presents areas of



FIG. 49. Osteopokily ; similar changes were present throughout the skeleton.

DISEASES OF BONES

greatly increased density, which render it very evident on radiography. The compact bone is involved first, and later the sclerosis encroaches on the marrow cavity, almost obliterating it. The remainder of the skeleton may be normal or show a certain amount of widespread osteoporosis. In a few cases there is an evident disturbance of calcium metabolism, and there may be calcium deposits in the kidneys or the soft tissues generally.

The term "marble bones" is a misnomer. "Chalky bones" would be preferable, for the affected bones though sclerotic are friable, and a pathological fracture is a common complication.

Osteopoikily (speckled bones) is an affection of a kindred nature, characterized by the development of multiple small rounded foci of dense sclerosis, lying within the substance of bones which in other respects appear healthy (Fig. 49).

ACHONDROPLASIA (*Chondrodystrophia Foetalis*)

This disease, which arises in intra-uterine life, is characterized by disturbance of the normal process of endochondral ossification, which leads to dwarfing and to certain remarkable deformities. The growth disturbance is believed to occur between the third and the sixth month of foetal life, and its effects are limited chiefly to those parts of the skeleton in which endochondral ossification is in progress at that period. Sometimes the disease is inherited, and often it affects several members of a family.

The subject of achondroplasia is rarely more than 4 feet 6 inches in height, but the trunk is well developed, and the dwarfing is due almost entirely to shortness of the extremities. Both upper and lower extremities are short, and contrast grotesquely with the trunk. The arms are so short that the finger tips may not reach the trochanters.

The long bones are especially affected. They are sometimes little more than two-thirds the normal length, but they are broad and well calcified. The epiphyses are always enlarged, sometimes greatly so, and may be of irregular shape. Fusion of the epiphyses with the diaphyses may be premature, but often it is delayed, and may even fail to occur.

Microscopic examination usually shows that the epiphysial cartilage is narrow and the zone of proliferation is absent, and instead of the usual clumps of cartilage cells there are small groups of cells separated by intercellular substance. Fibrous tissue, cysts, mucoid areas and dense bone may be observed in various combinations. For this reason there is arrest of the normal growth in length of the long bones which remain of more or less equal size; the epiphyses grow normally, and are therefore proportionately greater in size than the diaphyses. Often the bones are bent in an exaggeration of the normal curves, and for this reason knock-knee is common.

The head is large, rounded and brachycephalic, with prominent frontal and parietal eminences, and the nose is characteristically short, flattened and depressed at the base. These deformities of the skull result from failure of development of the cartilage-formed bones at the base of the skull. Failure of growth of the base of the skull limits the space available for accommodation of the base of the brain, but this is

compensated by an exaggerated growth of the membrane bones of the calvaria. The vertebral column may assume a deformity of lordosis, and the pelvis is usually narrowed in all its diameters. For this reason the pregnant achondroplastic is rarely delivered of a living child except by hysterotomy. The hands have a characteristic appearance, being short and broad, and the fingers are of almost equal length (trident hand). Delayed ossification is often apparent in the carpal bones, so that an achondroplastic child of ten or twelve years may have the carpal ossification normal for a child of one year. Achondroplastic dwarfs are readily distinguishable from cretins and mongoloid imbeciles on account of their muscular and intellectual vigour. Moreover, their sexual development is normal, or sometimes precocious.

OSTEOCHONDRITIS JUVENILIS

The term osteochondritis is used to denote a variety of conditions, described during the last few decades, which occur during childhood or adolescence and affect the epiphyses. The most familiar examples are those at the hip, the tibial tuberosity, the calcaneum, the tarsal navicular, and the vertebrae, but the disease is also known to occur in almost a score of other situations.

It is now generally believed that all these various lesions are but manifestations of some common fundamental process, modified in different situations by local factors. The lesions occur at a definite age period, which is determined by the time of appearance and fusion of the affected epiphysis, and they occur in epiphyses particularly subject to undue stresses and strain. Usually only one site is affected, but in a few cases more than one lesion has been observed.

The conditions have much in common. They occur more frequently in boys than in girls, and often follow slight trauma. The course of the lesion is characterized by a short active period, followed by resolution. Symptoms are usually mild and may sometimes be absent; in great contrast to this, the radiological features are always arresting.

Osteochondritis of the Hip (Legge-Calvé-Perthes). This is a disease of childhood and occurs most often between the ages of five and nine years. It is characterized by the signs of a fleeting synovitis and by a sequence of osseous changes which are out of all proportion to the mildness of the clinical features.

Platt has given a complete account of the clinical and radiographic manifestations of the disease. The first sign is usually a limp, insidious in origin and commonly painless, but occasionally accompanied by pain either at the hip or referred to the knee. A variable active period, sometimes with a mild pyrexia, is followed by a steady progress towards resolution. The joint usually presents only a slight limitation of the movements of abduction and medial rotation. Within these limits, movement causes no pain, and there is rarely any muscle rigidity or atrophy.

Radiographic examination shows that the disease affects the head and neck of the femur, and to a less extent the acetabulum.

In the femoral head the first change is a slight flattening of the epiphysis. Then the most characteristic change develops, an appearance

of "fragmentation" of the bony nucleus of the epiphysis into a number of bony islets interspersed with zones of osteoporosis. Presently the head becomes more flattened, and its margins become splayed out, mushroom fashion, beyond the rim of the acetabulum. At this stage the flattened, deformed, "fragmented" head gives a striking radiographic appearance, out of all proportion to the clinical symptoms. Later still, when the healing stage sets in, the decalcified areas disappear, the bony islets gradually coalesce, and the bone resumes its normal

density and trabeculation. The flattening deformity may remain, and even increase and lead to chronic arthritis.

In the neck of the femur the same cycle of osseous changes leads to softening of the bone, to broadening and shortening of the neck and to a degree of coxa vara. In the acetabulum the same changes may occur, leading to the adaptation of its articular surface to the altered shape of the head. The acetabular changes are entirely consequent to those of the head.

Histological and bacteriological investigations of the disease have been scanty. A few observers have obtained growths of staphylococci from cultures of excised

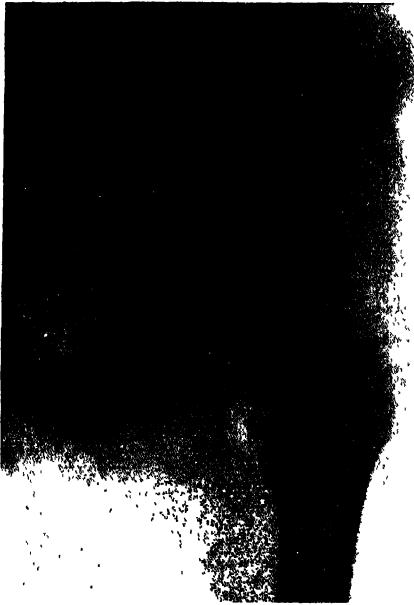


FIG. 50. Osteochondritis of hip (Legge-Calvé-Perthes). The femoral head shows the fragmentation and deformation characteristic of this disease.

portions of the femoral head, but these findings are offset by the negative bacteriological findings in other cases. On exposure of the joint, the synovial membrane has sometimes been found normal; in other cases a mild synovitis has been present and the joint has contained a slightly turbid, straw-coloured fluid. In a case reported by Perthes, histological examination of the epiphysis displayed what he regarded as a non-inflammatory replacement of cancellous bone by invading buds of cartilage. Phemister, on the other hand, described a case which, he considered, gave evidence of an old infective lesion, probably from an avirulent pyogenic organism.

Many theories have been advanced to account for the condition. It is now definitely recognized that tuberculosis, syphilis and rickets can be excluded, and there is no evidence that the disease owes its origin to endocrine derangement. At present two views hold the field: (a) that the disease is a low-grade inflammatory lesion, from avirulent organisms,

and (b) that the essential factor is trauma, either a single injury or perhaps repeated stresses and strains, followed by alterations in the blood supply to the area affected. This latter view is supported by the age and sex incidence of the disease, and by the history so commonly obtained of some definite though minor injury.

Tibial Apophysitis (Osgood, Schlatter). This is an osteochondritis affecting the tibial tuberosity, and it usually affects boys between the ages of twelve and sixteen years. It is essentially traumatic, a partial separation of the tuberosity as the result of sudden or excessive traction exerted through the fibres of the patellar tendon, or of a direct contusion of the part. The affection gives rise to mild discomfort and local swelling over the tubercle. Radiographically, the changes are similar to those at the hip. The bony nucleus of the apophysis is fragmented, and later becomes increasingly dense in a patchy manner. Its surface becomes irregular, and there is either a real or an apparent increase in the space between the apophysis and the diaphysis.

In the majority of subjects the tuberosity of the tibia develops as a tongue-like projection from the anterior part of the proximal tibial epiphysis, but in a proportion of cases the apophysis grows from a separate centre of ossification, which appears at the age of eleven years and usually fuses with the remainder of the epiphysis at from twelve to thirteen years. It has been suggested that osteochondritis is more prone to develop in those in whom this independent development occurs.

Osteochondritis of the Tarsal Navicular (Köhler). This condition occurs in younger children, between the ages of three and eight years. It has an insidious onset, with slight pain on walking, a limp and some pain and tenderness over the bone. An active period of variable duration is followed by resolution.

The characteristic radiographic picture shows a navicular smaller than its fellow, and of irregular outline. The bone is increased in density and the normal architecture of the bony trabeculae is lost. The general shape of the bone is altered, and the bone is flattened from before backwards without any lateral expansion.

The condition is usually regarded as the result of a mild inflammation. Clinically and radiographically in its early stages it is not unlike tuberculosis and immediate differentiation may not be possible.



FIG. 51. Tibial apophysitis.

Epiphysitis of the Calcaneum (Sever). This is a condition met with in adolescents, usually boys, between the ages of ten and thirteen, affecting the posterior epiphysis of the calcaneum. There are pain and limping of variable duration associated with difficulty in putting the heel to the ground. On radiographic examination, the same changes described in analogous affections elsewhere are noted. The calcaneal epiphysis appears narrow and irregular in shape, with great increase in bony density and a loss of the normal architecture. The lesion is probably traumatic in origin, the result of a direct injury or of repeated tearing strains exerted upon the growing bone by the muscles acting through the tendo calcaneus.

Vertebral Epiphysitis (Scheuermann-Calvé). This disease affects the upper and lower surfaces of the vertebral bodies. It has been described as occurring at various ages from ten to twenty-one, and it usually affects several vertebræ, not necessarily contiguous, in the thoracic or upper lumbar regions.

The upper and lower margins of the vertebral bodies are increased in density and of irregular outline, as though eroded. The width of the intervertebral cartilage is diminished and there may be in addition some deformity of individual vertebræ, which may assume a cuneiform shape. The disease is manifested by slight pain and weakness in the back, often with some scoliosis or kyphosis. There is tenderness over the spines of the affected vertebræ, but little or no limitation of movement, and no muscular rigidity or atrophy. The disease is to be distinguished from tuberculosis by these clinical and radiological criteria, and by the response to treatment.

POST-TRAUMATIC OSTEODYSTROPHY

Following injuries to the wrist, ankle and foot, and less often larger joints, the adjacent bones may sometimes undergo progressive decalcification, which is associated with much pain and disability—*post-traumatic painful osteoporosis* or Sudek's atrophy.

The osteodystrophy may be the outcome of a fracture such as Colles' at the wrist or a Pott's fracture at the ankle, but quite frequently it follows lesser injuries such as a contusion or a wrench of the soft tissues. It has been observed after infections, burns and scalds, and operations.

The poly-articular regions of the carpus and tarsus are most frequently affected, less often the shoulder and knee joints. At the wrist or ankle the decalcification is observed first in the small bones, and later in the bases of metacarpals or metatarsals. The cancellous bone of the lower end of the radius or the tibia may participate, to a lesser extent, in the porosis, but the diaphysis escapes. The osteoporosis may progress during many months and may be permanent; or very gradual, but usually incomplete, recalcification may occur. Full restoration of function seldom occurs: in the foot a variety of traumatic flat-foot may develop. The sequence of changes, as observed radiographically, is as follows: (1) In the early stages, irregular areas of decalcification producing a "stippled" appearance; (2) later (usually after several months), disappearance of the trabeculæ resulting in a structureless

"glassy" appearance, a shell only representing the contour of the affected bones; and (3) finally (in progressive cases), fusion of the affected bones into a conglomerate mass: calcification or ossification in the articular ligaments is frequently observed at this stage.

The clinical features of this type of osteodystrophy constitute what is now a well-recognized syndrome, characterized by severe and per-



FIG. 52. Radiographic appearances of post-traumatic osteodystrophy affecting the bones of the foot: a film of a normal foot (right) is for comparison. The osteoporosis involves the tarsal bones and the extremities of the metatarsals: the shafts of the metatarsal bones are little affected.

sisting pain, stiffness of the affected joint, and local vasomotor disturbances. The pain is prolonged and its severity is out of proportion to the nature of the causal injury: it is aggravated by movement and is not relieved by immobilization. Stiffness and loss of function are probably the outcome of pain and associated muscle spasm. The vasomotor phenomena are of special interest: the part remains cold, and for long retains a dusky cyanotic tinge, and the skin is glossy and the subcutaneous tissues oedematous. In the early stage sour sweat is exuded in excessive quantities.

The ætiology of this variety of osteodystrophy does not admit of ready explanation. The decalcification suggests that hyperæmia has been prolonged and exaggerated. So far as can be deduced the initial trauma promotes an abnormal reflex in the autonomic innervation of the affected part, whereby afferent pain-bearing impulses are transmitted to reflex centres which, in turn, convey vasomotor and other efferent stimuli, resulting in sustained vasodilatation peripherally—possibly the result of excessive production of histamine locally. Probably a vicious circle is established: local hyperæmia keeps up pain and the pain (reflexly) maintains hyperæmia. The benefit which may follow sympathetic denervation of the part, though logically it might be expected to exaggerate hyperæmia, probably owes its effects to the abolition of the excitator influences of painful stimuli from the injured part.

POST-TRAUMATIC SPONDYLITIS (Kümmell, Verneuil)

This affection was mentioned by Verneuil in 1892 and described in more detail by Kümmell in 1894. It is a delayed sequel to injury of the spine, and it is characterized by progressive decalcification of a single vertebral body, with consequent collapse of the body and the production of a kyphosis. The condition is almost limited to the male sex and it is commonest in early adult life, though not unknown either in childhood or in middle age.



FIG. 53. Post-traumatic spondylitis. Extreme decalcification of the first lumbar vertebra, with subsequent collapse of the spine and an angular kyphosis. In this case the affection was a late sequel to a fall from a ladder.

The initial injury is a forcible flexion of the spine, such as may cause compression of the vertebral bodies. It usually arises from the impact of heavy weights upon the bent shoulders, for example, in pit accidents, the force being then transmitted through the concavity of the spinal column and exercising its compressive effect upon the lower thoracic or upper lumbar vertebræ. In other cases the injury results from falls from a height, the force being then transmitted upwards from the feet or buttocks and exercising the same effect upon the spine. The initial injury is not necessarily a severe one, and the dystrophy has been known to follow such trivial accidents as arise from jumping from a slowly moving vehicle.

In most cases at the time of injury there is clear evidence of damage to the affected vertebræ, a compression

fracture of minor degree, and sometimes there is a temporary paraplegia or other evidence of cord involvement. In others the immediate symptoms are mild and transitory. Sometimes clinical and radiological examinations fail to reveal any gross lesion of the vertebræ, but it seems likely that in all cases some small degree of damage has occurred, and in the great majority a complete radiological investigation with modern apparatus would reveal some small lesion.

Following the injury there is an interval of several months or even years during which subjective symptoms and signs are absent. The dystrophy becomes manifest subsequently, and attention is usually drawn to it by pain, with weakness of the lower limbs and eventually, in some cases, progressive paresis culminating in paraplegia. Examination carried out at this time reveals a striking deviation from the normal. An angular kyphosis is usually present, and radiological investigation shows that this is the result of collapse of the affected vertebral body, which is decalcified to an extreme degree.

The fundamental feature of the disease is a post-traumatic decalcification, and there is much to suggest that the affection is similar to the decalcification which follows injuries to the carpal lunate or other bones. It has been suggested that the vertebral dystrophy is the result of a trophic disturbance following injury to the nerves of the affected vertebra, but it seems more probable that the fundamental factor is some alteration of the nutrition of the bone.

POST-TRAUMATIC CARPAL DYSTROPHY

In 1910, Kienböck described the affection of the carpal lunate bone now generally known by his name, a late sequel of injury to the bone which is characterized by alteration in the structure of the bone with irregular patchy decalcification and subsequent sclerosis. Since then similar affections have been observed, though less commonly, in the navicular and other bones of the carpus, and in the metacarpus.

The dystrophy of the lunate bone, being, at least in the great majority of cases, a result of injury, is naturally commoner in males than in females, the proportion being about seven to one. For the same reason it is fully twice as common in the right as in the left wrist. The injury may be either a sudden severe blow, such as may be occasioned by a fall on the outstretched hand or repeated minor injuries. In some cases there has been a suspicion that the initial injury amounted to an unrecognised fracture or a momentary, spontaneously reduced, dislocation.

The dystrophy does not immediately succeed the injury, but becomes apparent after an interval of several weeks or months, during which the disabling effects of the injury may have subsided. The dystrophy manifests itself in a recurrence of the disability, with fixation of the wrist, swelling over the dorsal aspect, and local pain either on pressure or on movement. In some cases pain over the lunate bone may be elicited by axial percussion of the head of the third metacarpal. From diminution in the size of the lunate bone this metacarpal may attain an unduly proximal position in the hand, with diminution of prominence of the metacarpal head.

Radiological examination reveals a characteristic change in the form and structure of the lunate. The bone is narrowed, and in place of the normal uniformity there is an irregular, patchy increase in the density of the bone shadow. In some cases the denser patches are interspersed by areas of diminished density, and sometimes the appearance closely resembles that of a fracture of the bone. In addition, there may be the changes characteristic of osteo-arthritis of the neighbouring joint surfaces.

The cause of the dystrophy is not yet clearly established. Kienböck attributed it to rupture of blood vessels caused by momentary dislocation of the bone, but such a gross injury can only be responsible in a small proportion. In some cases it seems rational to presume that the dystrophy results from some less obvious interference with the vascularity of the bone.

METATARSAL DYSTROPHIES

The forefoot has undergone fundamental changes during the evolution of orthograde man from his primitive arboreal stock, in order to render the foot able to take the body weight during standing and walking. It seems likely that an atavistic structural anomaly of the forefoot, by predisposing to strain, may be a factor in the ætiology of a number of diseases characterized by metatarsal pain. In a recent paper Bruce has put forward evidence for including such widely differing conditions as metatarsalgia (Morton's Disease), marching foot (Deutschländer's Disease) and the Köhler-Freiberg disease of the metatarsals in this single group.

The Primary Anomaly. In the pronograde foot of apes, adapted for prehension, the hallux is thumb-like, with a short metatarsal bone widely abducted in the varus position and very mobile in relation to the other metatarsal bones. During evolution towards the human form the hallux metatarsal becomes adducted towards the other toes, it becomes fixed in position, and its length approximates more closely to that of the other metatarsals. Coincidentally it becomes thickened and strengthened and assumes an important part in the formation of the longitudinal arch of the foot.

Quite commonly the first metatarsal bone presents a structural anomaly which may be regarded as an atavism; the bone is abducted to the varus position, is relatively short and possesses an exaggerated mobility (*metatarsus varus, brevis et mobilis*). This anomaly tends to weaken the longitudinal arch of the foot. The weakness may be compensated by bony hypertrophy or by an increase in muscle tone (especially of the adductor hallucis muscle, which serves to anchor the first metatarsal bone to the second, and the lumbricals and interossei, which keep the small toes in contact with the ground and so diminish the load on the metatarsal heads). If, however, these compensatory mechanisms fail, as may occur from strain, overwork, illness or malnutrition, an increased strain is placed upon the forefoot and one or more of the following affections may develop. All of them are characterized by pain in the ball of the foot, swelling over the dorsum of the

metatarsal region, dorsiflexion of the metatarso-phalangeal joints, and pain on moving the toes.

Metatarsalgia (Morton's Disease). Two varieties of metatarsal pain are included under this term. The one, which is of neuralgic character, has been attributed variously to compression of a digital nerve between the contiguous heads of the metatarsal bones, or to traumatic inflammation of a small adventitious bursa sometimes found in this same situation. The other, which is of a constant, aching character and situated under the ball of the toes, is attributed to a strain of the metatarsal arch.

Marching Foot (Deutschländer's Disease). This very disabling condition occurs mainly in infantry recruits or in hikers and comes on after unusually strenuous marching. It has also occurred in those, such as nurses, whose occupation entails much standing. The disease affects one of the metatarsal bones, usually the second one, and it is characterized by the development of a mass of bone in relation to the middle of the metatarsal shaft. In most cases the metatarsal shaft presents a fracture at this level. Recent radiographic investigations indicate that the earliest feature is the formation of new bone under the periosteum around the shaft, and that later the shaft becomes decalcified and eventually undergoes fracture. It is thought that the essential ætiological factor is a bending strain imposed upon the delicate metatarsals in walking, as a result of strain of the forefoot induced by a metatarsus varus deformity.

Köhler-Freiberg Disease of the Metatarsal Heads. This affection, which must be distinguished from Köhler's disease of the tarsal navicular, is characterized by decalcification and collapse of the spongy bone immediately subjacent to the articular cartilage on the dorsal aspect of the head of one of the metatarsals, generally the second. The affected bone may form a loose fragment and be set free in the proximal toe joint. A hammer-toe deformity is often present, and it has been suggested that minor trauma acting along the line of the first phalanx constitutes an ætiological factor, superimposed upon the strains associated with a decompensated metatarsus varus.

Dystrophic (Fatigue) Fracture. Bone changes similar to the above have been observed in the long bones, especially in the upper third of the tibia and the distal end of the fibula. In the tibia the change is marked by a zone of rarefaction in the shaft of the bone some 2 to 3 inches from the epiphysis, with a variable amount of new bone formation at the same level on the outer, less often the inner, aspect of the tibia. In rare instances, if untreated, it culminates in complete fracture.

The origin of the dystrophy, which has received the title of "fatigue fracture," is a matter of conjecture. It is believed to result from prolonged stress at the affected part of the bone.

RICKETS

The word "rickets" is probably derived from the Old English "wrickken" ("to twist"), and it describes well the skeletal deformities that constitute such a striking outcome of the disease. From the

surgeon's point of view, rickets is sometimes regarded as entirely a disease of bones, but actually the bony lesions form only one aspect of a general constitutional disorder that affects almost every system of the body, and the early symptoms are more often related to the gastrointestinal tract or the general health than to the bones.

Rickets is now known to be due to deprivation of vitamin D. In Great Britain formerly it was common among children of the poorer

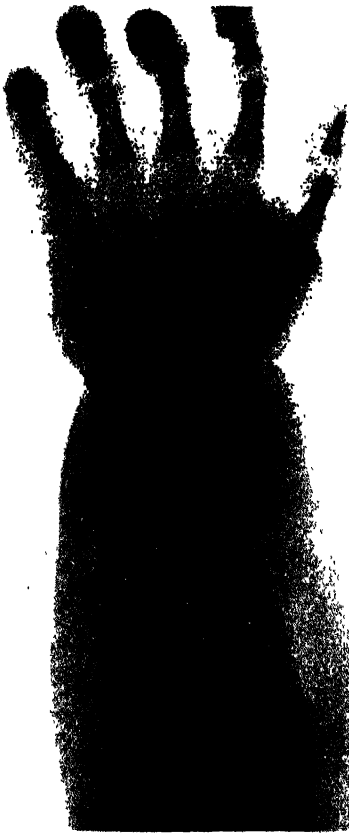


FIG. 54. Active rickets in a young child. Radiograph showing broadening and irregularity of the metaphyses.

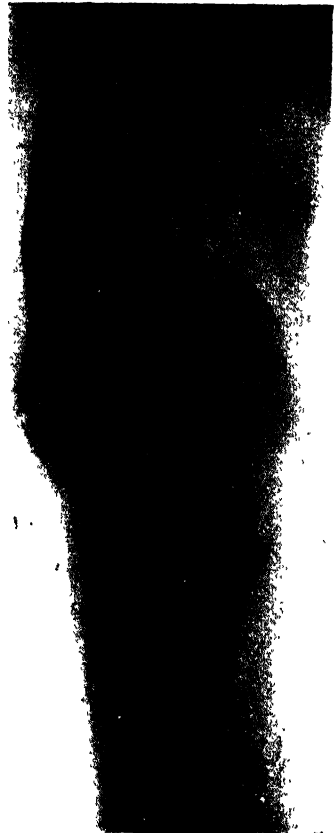


FIG. 55. Rickets affecting knee region. Radiograph showing broadening and irregularity of metaphyseal regions and secondary bowing of femur.

classes, whose diet was deficient, and especially in the large towns where the ultra-violet rays of sunlight are filtered off by the smoke pall. Since about 1917, when cod liver oil and other vitamin-rich preparations came into general use for infant feeding, the disease in its active form has almost disappeared.

Rickets begins usually between the ages of six months and two years. After a variable period, a few months or a year or so, the active phase of the disease may cease, but its effects upon the skeleton remain, either

as obvious deformities of the extremities, thorax and skull, or as less obvious deformities of the pelvis.

In the active phase of the disease the child is anæmic and wasted. There is a general enlargement of lymph glands and of the spleen, and this, with much muscular hypotonicity, causes the characteristic protuberant "pot belly." Often there are recurring attacks of bronchitis and of diarrhœa, and there may be such nervous symptoms as tetany or convulsions.

Changes in the Bones. The rôle of vitamin D is to facilitate the

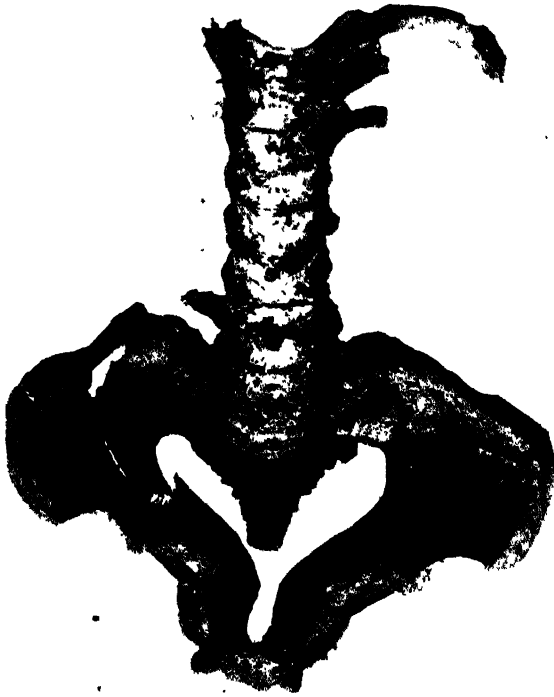


FIG. 56. Rickety deformity of the pelvis. The pelvic bones are beaked anteriorly, the acetabula are displaced medially, and the pelvic aperture has assumed a trefoil shape. The sacrum has rotated under the body weight, and the promontory is projected anteriorly.

(Museum of Royal College of Surgeons of Edinburgh.)

absorption of fats from the alimentary tract and thus to promote the absorption of calcium phosphate. When it is lacking, osteogenesis is impaired. Thus there is a temporary disturbance of the ossifying process, whereby the bone that is formed during the active phase of the disease is evolved very irregularly and is soft, pliable and readily deformed. The bone formed before the onset of the disease is relatively little affected; after the disease has run its course the normal process of bone formation is resumed; but that part of the bone laid down during the florid stage of the disease for long remains obvious.

If a longitudinal cut be made at the end of a healthy growing bone

the site of bone growth is represented by a thin white transverse line, which marks the orderly replacement of cartilage by bone. In rickets the appearance is very different. In place of the thin white calcified line there is a broad pale yellow area, soft and devoid of calcium. In this broad strip the ossifying process is totally disordered, and irregular islets of unchanged cartilage alternate with areas of imperfectly formed bone. In addition, the whole region of ossification is expanded laterally and swollen, and under the stresses of weight-bearing or muscular activity the softened bone often becomes bent or curved.

Enlargement of the growth regions and curvatures constitute the principal macroscopic changes. In addition, the whole skeleton is often stunted.

At the costochondral junctions there develop raised bead-like nodules



FIG. 57. Endochondral ossification in rickets. A microscopic section of the costochondral junction of a rickety puppy (low power). (a) Pre-formed hyaline cartilage. (b) Zone of proliferation of cartilage cells. (c) Newly formed bone trabeculae. The whole region of ossification is enlarged and deformed. The cartilage cells have proliferated irregularly and persist in islands among the bone trabeculae. The trabeculae are almost devoid of calcium.

which project both superficially under the skin and deeply towards the thoracic cavity, the rickety rosary. A "pigeon-breast" deformity sometimes results from bending or infraction of the ribs from the stresses of respiratory movements, and a horizontal sulcus (Harrison's sulcus) may appear, from traction on the soft ribs.

The long bones in rickets are often bent, especially in children who are not too feeble to crawl or walk. In the femur the natural curves are exaggerated and the bone is bowed both forwards and laterally. Yielding of the femoral neck under the body weight may lead to a severe degree of coxa vara. The tibia is often bent both anteriorly and laterally, and a pronounced degree of bow-leg may result. Occasionally the reverse deformity, knock-knee, occurs, and rarely one limb is bent inwards, the other out. The growing ends of the long bones become swollen. This is often especially distinct at the distal ends of the radius and tibia,

particularly if the child has been allowed to support its weight on these bones.

The pelvis, which is subject to so many stresses from adoption of the upright position, becomes greatly deformed if the child is allowed to stand. Two principal types of deformity are recognized. Most often there is a flattening of the whole pelvis, with diminution in the conjugate diameter; rarely the pelvis assumes a trefoil shape like that seen in osteomalacia. Either of these deformities may be an impediment to the passage of the foetal head during parturition.

The skull becomes broadened, from the formation of much soft osteoid tissue under the pericranium. The forehead is square and broad, and large bosses develop over the frontal and parietal tuberosities. The *vertebral column* is affected (hence the name *rachitis* which is sometimes applied to the disease), and from softening of the bones and laxity of the soft parts there develops either kyphosis or, more often, scoliosis. Lastly, *dentition* is delayed, and calcification of the teeth is defective.

Microscopic Appearances. Rickets affects principally those parts of the bones that are actively growing, and the process is therefore most obvious near the ends of long bones; to a less extent it is seen also under the periosteum.

The microscopic changes characteristic of the process of endochondral ossification have already been described (*see* p. 109). In the normal process the most striking feature is the orderliness of the changes, and this is manifest in the regular arrangement of the different zones, from unchanged cartilage at one end, through the zones of cartilage-cell proliferation and of provisional calcification to that of actual bone formation.

The process in rickets is very different, for here all is disorder. The cartilage cells proliferate, sometimes to excess, but instead of forming straight columns they lie in irregular masses; the zone of provisional calcification is no longer a thin well-defined white line, but is uneven and indistinct; the invading capillaries run in all directions; the bone cells proliferate irregularly, and, since no calcium is available, only imperfectly calcified osteoid tissue is produced. Large islets of hyaline cartilage remain altogether unaltered, and may persist in regions normally occupied by fully formed bone.

When the disease has run its course the first evidence of healing is the deposition of calcium, first as a thin irregular line of poor density, later in greater amount. That portion of the bone formed during the rickety period remains for a long time imperfectly calcified. Eventually, however, it heals, leaving little abnormality.

Appearance in Radiograms. Interpretation of the pathological process is greatly assisted by radiographic examination. By this method it is possible to distinguish two types of "florid" rickets. If the child has been too ill to support itself, there is seen the passive type of florid rickets. At the metaphysis there is a striking departure from the normal, and in place of a straight well-defined line of opacity separating bone from cartilage there is a broad irregularly blurred area. Since much of the newly formed osteoid tissue transmits the rays, the bone shadows of epiphysis and diaphysis are separated more widely than

usual, but there is no gross deformation or infraction. The active type of florid rickets is seen when the child has been able to crawl or walk. The epiphysial line is even more blurred and irregular than before, and since the soft osteoid tissue expands laterally when compressed by weight-bearing, the bone shadow is considerably broadened. Lack of calcium is more evident in the central axis of the bone than under the periosteum, and in radiograms this leads to an apparent scooping out of the end of the bone (cup-shaped deformity). Infraction of the cortical bone or actual green-stick fractures may sometimes be seen.

OSTEOMALACIA

In virtue of its derivation (*ὀστέον*, bone; *μαλακός*, soft), the term osteomalacia may be applied correctly to any condition of bone softening, but it is now by custom limited to one special type of affection. This is a generalized skeletal disease which almost always affects pregnant or parous women, especially women debilitated by inadequate food, restricted freedom, frequent pregnancies and prolonged lactation. Very occasionally men are affected (senile osteoporosis). A similar condition, "hunger osteomalacia," was prevalent in the starving population of Vienna during 1919-20, especially in middle-aged subjects of both sexes.



FIG. 58. Osteomalacia. The pelvis is greatly deformed and there is a bilateral coxa vara deformity. The ribs and the sternum are distorted.

(Museum of Royal College of Surgeons of Edinburgh.)

The disease is characterized by extreme decalcification of the bones, with consequent deformities from curvature or fracture. It usually commences during pregnancy and undergoes a remission at the termination of lactation, but the progress is greatly hastened by succeeding pregnancies and a fatal outcome is rarely delayed more than a few years.

The cause of osteomalacia is not yet definitely determined, and indeed it seems likely that there is no one cause, but a number of contributory factors. In the later months of pregnancy a large amount of calcium

is required for foetal ossification ; during lactation a large amount is lost in the milk ; and when for any reason the intake of calcium is diminished the necessary calcium is removed from the skeleton.

Thus the underlying causative factor in osteomalacia appears to be a deficient intake of calcium. This may result either from a faulty dietary or, more often, from impaired absorption in the intestinal tract. There is some evidence to suggest that in many cases the impaired absorption results from a lack of vitamin D, and osteomalacia is thus comparable to rickets.

Osteomalacia in gross form is rare in Great Britain and America, but it is not uncommon in certain parts of France, Austria, and Italy, and it is endemic over wide areas of Northern China and Northern India. The reasons for this distribution are not far to seek. In the north of China the diet is often deficient in calcium and in vitamins, and the severity of the winter and the practice of foot-binding combine to keep the women indoors. In India the observation of strict purdah entails close confinement, and the risk of cholera prevents the free use of fresh vegetables and fruits. Both in China and in India prolonged lactation is customary, and this results in great depletion of the calcium reserves.

Appearance of the Bones. The bones are decalcified to an extreme degree, and as a result they are soft, pliable, and readily cut with a knife. In some cases they may be bent or twisted with ease. On section it is seen that the bone is extremely porous. The trabeculae are eroded, and sometimes little osseous tissue remains except in the cortex. The marrow and all the interstices of the bone are filled with connective tissue of great vascularity.

Microscopic examination confirms the changes just described. The enlarged lacunae of the bone contain numerous large blood vessels with young fibrous tissue, and the bone trabeculae are narrowed or almost obliterated. A striking feature is the great paucity of calcium. The outer zones of the trabeculae are composed of osteoid tissue completely lacking in calcium, and such calcium as remains is concentrated in small deposits at the centre of the trabeculae.

The Deformities. Skeletal deformities constitute the most obvious feature in osteomalacia. All parts of the skeleton participate, but the deformities are most evident in the parts of the bones exposed to stresses from gravity or muscular action (so-called Looser's zones).

The pelvic bones are especially affected. The acetabula are forced medially from the pressure of the femoral heads, and the pubic bones become beaked anteriorly, the sacrum is rotated under the body weight and its promontory is projected forwards, and thus the upper pelvic aperture assumes a trefoil shape (*see* Fig. 56).

The bones of the lower extremity are usually deformed by weight bearing. The femur and tibia may become bowed with an antero-lateral convexity and coxa vara develops. The ribs are bent medially in their mid-portions, and the vertebrae may soften and collapse.

Death may be due to intercurrent pneumonia, or to complications during parturition, the result of the pelvic deformity.

OSTEITIS FIBROSA (Fibrous Osteodystrophy)

Osteitis fibrosa may occur as a generalized disease affecting the whole or the greater part of the skeleton, or as a localized affection of a

single bone. It may affect either sex, but is (twice as common in women as in men.) The generalized disease arises usually in early adult life; it runs a progressive course and it usually terminates fatally within a few years of the onset. The localized disease, on the other hand, usually commences in adolescence, and progresses slowly, and in some cases it may become stationary. In their pathological features, moreover, the two types differ somewhat, and they will therefore be described separately. The generalized type is the less common, but owing to the extensiveness of its manifestations and the more frequent opportunities for post-mortem investigation it has been studied much more closely than the localized type.



FIG. 59. Osteitis fibrosa of the femur. The bone is extensively replaced by vascular connective tissue and contains two cysts. A pathological fracture has united in faulty position, and the softened bone has become greatly deformed.

(Museum of Royal College of Surgeons of Edinburgh.)

Generalized Osteitis Fibrosa

This uncommon disease was first adequately described by v. Recklinghausen in 1891. It is characterized by (wide-

spread skeletal changes with decalcification and fibrosis of the bones, and often by the formation of cysts and tumours in the bones.) Recent investigations have shown that in the majority of cases the

disease results from hypersecretion of the parathyroid glands, usually due to a parathyroid tumour.

(1) **The Skeletal Changes.** The outstanding pathological change in the bones is decalcification, and it may proceed to extreme degrees. The cancellous bone is principally affected, but the cortex also shares in the process.)

As a consequence of the decalcification the bones are greatly softened and they are very liable to curvatures or fractures. Sometimes they are so soft as to be cut readily with a knife. The stresses caused by gravity and muscular action lead to gross deformities of the bones. The femora are bowed antero-laterally, *cōxa vara* develops, the tibia becomes convex anteriorly, the vertebral column becomes kyphotic, the ribs bend at their angles and produce a pigeon-breast deformity, and the pelvis may assume the trefoil shape of osteomalacia.

The bones are increased in girth but smooth on the surface and covered by normal periosteum. Cortex and cancellous bone are extremely spongy and their interstices are filled with soft vascular granulation tissue, which replaces the whole fatty marrow. Microscopically, the trabeculae and lamellae are lacking in calcium



FIG. 60. Osteitis fibrosa. The bone trabeculae are reduced in size, and the intervening spaces are occupied by vascular fibrous tissue. There are numerous giant cells of osteoclast type, mainly situated in apposition to the bone trabeculae.

(Laboratory of Royal College of Physicians of Edinburgh.)

and are greatly reduced in size. The lacunae, which are correspondingly enlarged, are filled by vascular young connective tissue in which are numerous multinucleated giant cells of "osteoclast" type. In places there is evidence of the formation of new bone, which is almost devoid of calcium (osteoid tissue).

Cysts of various size, sometimes as large as a golf ball, are usually present, probably as a result of degenerative changes. They contain brownish, watery fluid or gelatinous material.) When large they render the bone very liable to fracture.

In many cases multiple tumours are also present in the affected bones. The tumours are solid or partly cystic, and of brownish or reddish colour, and microscopic examination shows that they have the characters of giant cell tumours (*see* p. 163). The tumours are usually of small size, but one or more may enlarge and attain considerable dimensions. They usually pursue a non-malignant course, but

occasionally they may undergo sarcomatous change. The tumours of osteitis fibrosa present one of the most interesting problems in the whole field of oncology, for they have all the characteristics of true neoplasms, yet are apparently an end-result of the excessive production of parathyroid hormones.

(2) **Hyperparathyroidism in Osteitis Fibrosa.** It is now recognized that in most cases the skeletal changes characteristic of osteitis fibrosa occur as a secondary result of over-activity of the parathyroid glands. Generally, an adenoma of one of the parathyroid glands is responsible for increasing the output of parathormone. The tumour may be in a

normally placed gland, or may be situated as high as the base of the skull or as low as the mediastinum. It is often of small size, or may be as large as 7 cm. in the long axis. Less often there is no tumour but a diffuse hyperplasia of one or more of the glands.

Hyperparathyroidism is believed to cause decalcification of the skeleton in virtue of its effect upon the inorganic phosphates of the blood. Its first effect is to cause excretion of phosphates and thus to reduce the ionic phosphate content of the blood. For the reasons discussed on p. 111, this demands a corresponding increase in the ionic calcium of the blood, which is effected by liberation of calcium from the skeleton.)

Thus while the bones become progressively rarefied, the calcium content of the blood is increased, from the normal figure of 10 mgm. per cent. to 12 mgm. per cent., or even to over 20 mgm. per cent. As a secondary result, calcium "overflows" into the urine, and the urinary calcium may be increased to eight times the



FIG. 61. Osteitis fibrosa cystica. The shaft of the femur is broadened and decalcified. The cortex is thin and the distinction between cortex and medulla is lost.

(By courtesy of Dr. Scott Park.)

normal amount. Often this leads to the formation of urinary stones. In a few cases the excess of calcium is deposited in certain tissues, notably the kidney and the stomach wall.

It should be mentioned that in a small proportion of cases osteitis fibrosa cannot definitely be attributed to hyperparathyroidism, and is of unknown aetiology. For this reason, parathyroidectomy should only be advised if there is definite evidence of hyperparathyroidism. In most cases increase in the calcium content with diminution in the inorganic phosphate content of the blood puts the matter beyond doubt. There have been, however, a few recorded examples of undoubted parathyroid osteitis in which such abnormalities could not be detected, and in which an increase in the calcium content of the urine was the only evident biochemical abnormality.

Localized Osteitis Fibrosa

This affection is considerably more common than the generalized disease and it differs greatly in its course. It arises usually in adolescence, progresses slowly over a period of several years and often undergoes remission. A single bone is usually affected, or rarely two or three bones. The upper end of the femur is the commonest site, less often the humerus or tibia, but no bone is immune. The first part of the bone to be affected is the metaphysis, and from here the disease spreads down the shaft. It rarely involves more than half the length of the shaft, and the epiphysis usually remains free. Cysts of various size are usually present, and occasionally almost the whole affected area is replaced by a single large cyst (one type of simple bone cyst).

The cysts render the bone very liable to fracture, but in spite of the lack of available calcium the fracture may heal with firm bony union, though slowly. The stimulus of the fracture may lead to arrest of the disease.

Localized osteitis fibrosa differs from the generalized form in that it has no evident relation to parathyroid disorders or to disturbances of calcium metabolism. Parathyroid overgrowths have not been observed, the blood calcium is normal, and there is no disturbance of the calcium balance.



FIG. 62. Osteitis deformans. Paget's original case. A man aged sixty-eight years, who had suffered from pains in the limbs during twenty-two years. Eventually a sarcoma of the radius developed. Note the curvatures of the vertebral column and lower limbs, and the large size of the head. (After Paget.)

OSTEITIS DEFORMANS (Paget's Disease)

In 1876, Paget described a generalized affection of the skeleton occurring in middle-aged or elderly subjects of either sex and characterized at first by decalcification of the bones with softening and curvature, and subsequently by recalcification and hardening of the bones. Every bone is affected to a greater or less degree, but the principal changes are generally seen in the bones of the lower extremity, the skull, spine, and clavicles. A similar disease sometimes occurs which involves a single bone or a few related bones, the remainder of the skeleton being unaffected.

The affected bones are increased in thickness, and, becoming



FIG. 63. Osteitis deformans. The calvarium from Paget's original case. Note the great increase in the thickness and density of the bone. (After Paget.)

softened, undergo deformation. The tibia becomes convex anteriorly, the femur bows forwards and laterally, coxa vara develops, and the patient becomes broad-hipped, bow-legged and bent.



FIG. 64. Osteitis deformans. The femur from Paget's original case. Note the coxa vara deformity, and the great increase in thickness and density of the bone. (After Paget.)

The surface of the bone in its final stage is rough and deeply furrowed, and extensively pitted. The periosteum does not appear to take part in the disease and is not thickened, but it is often firmly adherent to the underlying bone.

On longitudinal section the most striking feature is a loss of the normal distinction between compact and cancellous bone. At first the whole bone is spongy, and both the bone spaces and the marrow cavity are filled with vascular connective tissue. Later, as the vascularity dies down the texture becomes more solid, and the bone is "more compact looking, and dense like limestone" (Paget). Finally, near the surface the bone may assume an ivory-like sclerosis, but this is a rare change and is limited to small areas. Small cysts containing yellow or reddish gelatinous material may occur.

The skull is always affected in some degree. The disease involves the cranium principally, and the bones of the face are but little affected. The base of the skull sometimes participates but may remain unaffected. The bones of the vault show an increase in thickness, sometimes to as much as 2 cm. Such enlargement is responsible for one of the first signs of the disease, a progressive increase in the size of the cranial circumference.

The increase in thickness does not cause the cranial cavity to be reduced in size, but sometimes the frontal air sinuses are encroached

upon. The diploë of the flat bones is narrowed, or may even be obliterated. The bone is at first soft and vascular, and in the macerated specimen the sponginess is so great that water poured into the calvaria flows readily to the exterior. Later the bone becomes dense and hard.

In the vertebral column similar pathological changes occur, and from the generalized softening the whole column becomes shortened and bent. A regular anterior concavity of the whole spine commonly develops. The vertebral changes, together with deformities of the femora and tibiæ, bring about a progressive diminution in stature, even to the extent of a foot. A further result of the vertebral changes is a narrowing of the vertebral canal, and in rare cases this may lead to compression paraplegia.

In the upper limbs, the clavicle, humerus and ulna are the bones most obviously affected. The clavicle becomes thick, and an exaggeration of its normal curves leads to undue prominence. The humerus and ulna may become curved with a posterior convexity. With the bending of the trunk and lower limbs there is a relative elongation of the upper limbs, and the attitude of the patient may finally bear a striking resemblance to that of an anthropoid ape.

Microscopic Appearances. The microscopic appearance of osteitis deformans varies at different stages of the disease. At an early stage decalcification predominates, and the thickness of the lamellæ is decreased. The bone lacunæ are enlarged and are filled with vascular connective tissue, which often contains giant cells of "osteoclast" type. At a later stage new bone formation is seen. The new bone is formed on a different plan from the old, and lacks the regular arrangement of normal bone. The lamellæ are formed without regard to functional stresses, and Haversian systems are irregularly disposed.

Course of the Disease. Osteitis deformans is a disease of insidious onset and slow progress, and often first comes to notice on the occurrence of curvature or fracture of one of the affected bones. In other cases the increase in the size of the head leads to its recognition. Occasionally the excessive sclerosis of small areas of the bones may culminate in sequestrum formation, and with the access of mild infection an ulcer may result. Sarcomatous change is not uncommon, and is said to occur in 5% of cases.

Pathogenesis. Little definite is known about the cause of osteitis deformans. It appears certain that the disease is not hereditary, that it is not related to syphilis or other specific diseases, and that it is not a bacterial infection. The generalized distribution of the pathological changes strongly suggests that the fundamental factor is some disturbance of the endocrine control of bone metabolism. Kay has shown that the enzyme phosphatase is constantly present in excess, but this is not a characteristic feature, for it is present in any form of generalized skeletal decalcification.

The pathological process of osteitis deformans has been compared to that of osteitis fibrosa, and it will be noted that there is the same sequence of events, primary vascularization and decalcification, followed later by new formation of bone; but in osteitis deformans

the ultimate new bone is much more abundant and more diffusely distributed.

CYSTS IN BONE

The following varieties of cyst may arise in bones : (1) solitary or simple cysts, (2) cysts in bone tumours, (3) cysts associated with osteitis fibrosa, (4) hydatid cysts.

Solitary or simple bone cysts arise most often in childhood or adolescence. They are situated generally in the humerus, and they rarely affect other bones. The cyst usually arises in the region of the proximal metaphysis of the humerus, but as the bone elongates it gradually assumes a more distal position and ultimately may be situated several centimetres from the metaphysis.

The cyst may attain considerable size and the bone at the affected site may be reduced to a thin shell. It is then very liable to fracture. In some cases fracture appears to arrest the growth of the cyst and may allow of repair.

The cyst generally contains clear watery or slightly blood-stained fluid. It possesses no lining membrane and the wall is composed of fibrous tissue or bone. Often the cyst wall contains multinucleated giant cells of osteoclast type and the microscopic appearance may resemble that of osteitis fibrosa. Indeed, it seems probable that the two conditions are closely allied, and that simple cysts arise from a very circumscribed area of osteitis fibrosa in which degeneration and liquefaction predominate.

Cysts in bone tumours arise most often in connexion with giant-cell tumours, and often the greater part of the tumour becomes cystic (*see* Fig. 69). Generally such cysts contain blood-stained fluid or jelly-like material and are smooth walled. They possess no distinct lining membrane and the wall is composed of tumour tissue. Cysts arise also in chondromata, as a result of mucoid degeneration, and cysts may arise from degenerative changes in a sarcoma, myxoma and myeloma. Multiple cysts, especially in the marrow of the metacarpal bones and the phalanges, is an occasional feature of sarcoidosis. The condition has been styled "osteitis multiplex cystica."

Hydatid cysts of bones, and cysts associated with osteitis fibrosa, are described on pp. 52 and 151 respectively.

XANTHOMATOSIS OF BONES (Skeletal Lipoid Granulomatosis)

Cases of this remarkable disease were described, under various titles, by Thomas Smith in 1865, and later by Hand, by Schüller and by Christian, but its true nature was not understood until 1925.

It is characterized by the development of multiple tumours in certain bones, and, in most cases, by exophthalmos, diabetes insipidus, and inflammation of the mouth and gums. Occasionally the disease has been associated with dwarfism, jaundice, and dystrophy of the adiposogenital type.

The disease occurs most often in young children, but is encountered occasionally in adults. There is no evidence of a racial or familial

incidence. In approximately one-third of the cases, the disease progresses and soon proves fatal. In the remainder, spontaneous remissions occur, and if early treatment is instituted, especially by adequate X-ray therapy, the progress may be arrested and complete healing ultimately achieved.

The Bony Lesions. The most characteristic feature of the disease is the development of multiple tumours of xanthomatous type. In the great majority of cases the tumours are limited to bones formed in membrane, especially the cranial bones and the mandible. Less often the



FIG. 65. Xanthomatosis of bones. The radiogram shows the characteristic defects in the bones of the skull.

(By courtesy of Professor Sir John Fraser.)

scapula and pelvis are involved, rarely the long bones of the extremities.

The tumours are multiple, rounded and well circumscribed. In some cases they are palpable under the scalp, or they may cause exophthalmos or other pressure effects. They are readily recognizable on X-ray examination, which demonstrates large, irregularly rounded defects in the bones, not unlike the lesions characteristic of osteitis fibrosa.

The microscopic appearance of the tumours is closely similar to that of xanthoma in the skin and subcutaneous tissues. The tumours are composed mainly of large endothelial cells, with small, dark, rounded nuclei and a delicate reticular cytoplasm. These "foamy" cells owe their appearance to the presence of numerous minute globules of cholesterol esters, lying within the cytoplasmic network.

When healing takes place, either by spontaneous remission or as a

result of X-ray therapy, the lipid-laden cells are replaced by young fibrous tissue, and later by new bone, so that eventually it may be difficult on X-ray examination to recognize where the tumours had been situated.

The Other Lesions. In a small proportion of cases the bone lesions form the only recognizable feature of the disease. More commonly, one or more of the following disorders coexist.

Exophthalmos is present in more than half the cases. It may be an early feature, and is probably due to forward displacement of the eyeball by a xanthomatous tumour arising in the wall of the orbit.

Diabetes insipidus is almost equally common. In a few cases it appears to be due to pressure by a xanthomatous tumour in the region of the sella turcica, but more often there is no evidence of this, and the cause and significance of the polyuria remain in doubt.

Gingivitis and *stomatitis* occur less often, usually in association with xanthomatous tumours of the mandible. Their clinical importance arises from the fact that tenderness along the gums, with loosening of the teeth, may afford the earliest evidence of the disease.

The pathogenesis is not clearly understood. In view of the frequent association with diabetes insipidus, a primary affection of the hypophysis or midbrain has been suggested. On the other hand, the nature of the cholesterol-laden deposits suggests that a disturbance of the lipid metabolism is at fault. The blood cholesterol content in most of the recorded cases, however, has been within the limits of normal, and it must be admitted that at present there is no direct evidence of a metabolic disorder.

PRIMARY TUMOURS IN BONE

SIMPLE TUMOURS

The classification of simple tumours arising from the skeleton is complicated, and many lesions are often designated as tumours that have really no claim to this title. Confusion has arisen from the fact that such terms as osteoma and chondroma have in the past been applied loosely to any bony or cartilaginous swelling irrespective of its exact mode or site of origin. Thus "osteoma" is often used synonymously with "exostosis" for any bony mass projecting from the skeleton, and it has even been applied to the new bone formed in so-called myositis ossificans and various other diseases. Similarly "chondroma" has been applied to the cartilaginous projections of chronic arthritis or of diaphysial aclasis. Increasing knowledge of the pathological processes of many such lesions has led to their exclusion from the category of neoplasms, and others at present retained will no doubt follow in the course of time, so that eventually the group of simple bone tumours may shrink still further.

Osteoma

Compact Osteoma (Ivory Exostosis). This rare tumour occurs most often in relation to the skull bones, especially the frontal or

parietal bones. It may project on the outer aspect of the skull, where it forms a smooth rounded or conical projection under the scalp, or it may grow into the frontal sinus or project from the frontal bone into the orbit. Rarely it grows from the inner table of the skull and indents the brain, and occasionally it lies in relation to the external acoustic meatus or inside the maxillary air sinus.

The tumour grows very slowly, but in the course of many years it may attain large proportions. At first it is round or hemispherical, but, with increase in size, it becomes irregular and somewhat lobulated. In consistence it is extremely hard throughout, and it may be polished like ivory. Its principal effects are from pressure upon neighbouring structures. When situated close to the skin it may lead to ulceration ; in the orbit, it may displace and destroy the eyeball and later protrude

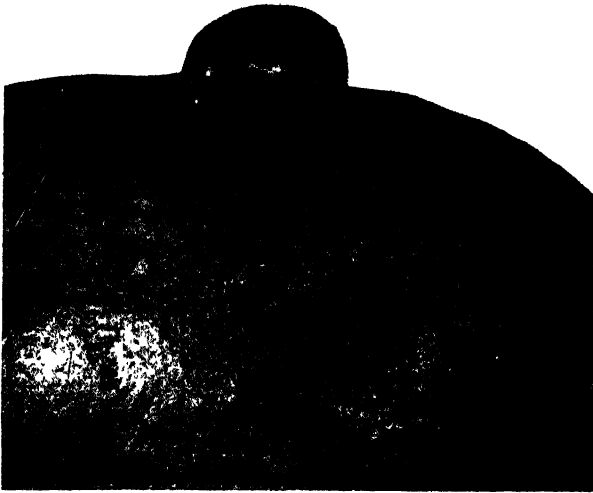


FIG. 66. Compact osteoma of the parietal bone. The tumour is smooth, rounded, and as hard as ivory.

(Department of Forensic Medicine, University of Edinburgh.)

on the surface ; in the acoustic meatus, it predisposes to infection and may cause deafness. It is of interest to note that a large osteoma may separate spontaneously, presumably from interference with its nutrition. Bland Sutton has recorded a case of an orbital osteoma which, after destroying the eyeball, finally shed itself spontaneously.

Similar in appearance to an osteoma, but actually an example of heterotopic ossification, is the bulky symmetrical intracranial osteophyte affecting the dural aspect of each half of the frontal bone. It occurs most frequently in aged, debilitated or bedridden subjects, and is probably due to deposition of bone in the fluid-filled space resulting from recession of the brain and dura mater from the frontal bones as a result of prolonged recumbency. The bony masses produce no pathological effects.

The *puerperal intracranial osteophytes* ("hoar-frost osteophyte"), which coat the inner table of the skull with a veneer of new bone, are also

examples of ectopic bone formation, following upon deranged calcium metabolism. They are encountered as a rare complication of eclampsia or puerperal sepsis.

Cancellous Osteoma. It is doubtful whether this should be regarded as a true neoplasm or as a manifestation of some disturbance of bone growth closely allied to diaphysial aclasis (*see* p. 129). For this reason it is sometimes known as a *biotrophic osteoma*. It consists of a spur of cancellous bone, projecting from the neighbourhood of a metaphysis. The most common situation is in the neighbourhood of the knee, but almost any bone may be affected. From the time of its appearance in adolescence up to the age of twenty or twenty-five years, the osteoma is capped by a layer of hyaline cartilage, which is probably a displaced portion of the epiphysial cartilage. As it grows it becomes pedunculated and lies obliquely, directed away from the neighbouring epiphysis. In some cases the tumour is more sessile, irregular in shape, and with a massive cartilaginous cap. Such a tumour is sometimes called an *osteochondroma*.

At first the tumour is situated close to one margin of the epiphysial cartilage, but as the diaphysis increases in length it comes to lie nearer to the mid-point of the shaft. At about the time when the epiphyses of the parent bone fuse, the cartilaginous cap of the osteoma becomes ossified and the tumour then ceases to grow.

A cancellous osteoma may cause pain from pressure on a nerve, but often it is symptomless and is recognized only on chance examination. An adventitious bursa may form over it and may become inflamed. Rarely the osteoma may be fractured from minor degrees of violence.

Other bony swellings, sometimes termed osteoma, are described in other chapters (*see* "Traumatic Osteoma," p. 220).

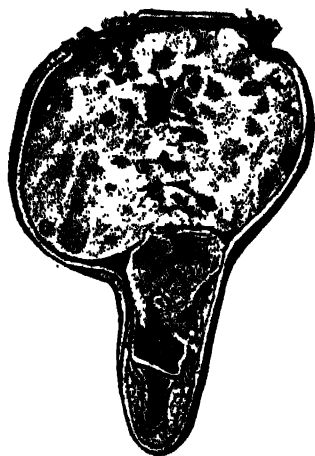


FIG. 67. Multiple chondromata of the index finger. The proximal phalanx is replaced by a rounded tumour, and the second phalanx contains a small one of similar appearance. Note the areas of mucoid degeneration.

(By courtesy of Mr. J. W. Struthers.)

Chondroma

As has been mentioned above, the term chondroma is applied loosely to many cartilage-containing swellings attached to the skeleton, regardless of their mode of origin. It has been applied, for example, to the cartilaginous masses that occur in dyschondroplasia or in rickets, and to those arising from the

synovial membrane and joint margins in chronic arthritis. It is doubtful if such masses, associated as they are with recognizable dystrophies or diseases, should be regarded as true neoplasms.

Chondromata arise usually from the metacarpal bones and the phalanges of the hands, and are then usually multiple. Often such

multiple chondromata occur in the subjects of diaphysial aclasis, a remarkable example of tumours arising on the basis of a generalized growth disturbance. Less commonly a chondroma arises from the scapula, ribs, pelvic bones, and long bones of the extremities. The tumours appear usually in childhood or adolescence and they grow slowly over a period of years. When general growth of the skeleton ends, the tumours may also become stationary.

Chondromata often grow near an epiphysial cartilage. At first they sometimes lie in the substance of the bone (enchondroma) and they may remain there, but as they increase in size they usually project under the periosteum (ecchondroma). One or more of the tumours may



FIG. 68. Multiple chondromata. A radiogram from a woman aged thirty-seven years, the subject of diaphysial aclasis. All the metacarpals and phalanges are affected by chondromata, some situated inside and expanding the bones, others projecting at the surface. Three of the larger tumours had undergone mucoid degeneration.

(Department of Surgery, University of Edinburgh.)

attain considerable size and may lead to much deformity and disability.

The growths are lobulated, smooth on the surface, and covered by a layer of fibrous tissue derived from the periosteum. Often a thin shell of bone is present, and there may be bony trabeculae between the lobules.

The microscopic appearance is like that of normal hyaline cartilage, but the cells are arranged irregularly and vary in size and shape. Necrosis or mucoid degeneration often takes place, and leads to one form of bone cyst. Calcification is common, and sometimes ossification occurs. Sarcomatous change is rare.

Giant-cell Tumour

(Tumeur à myeloplaxes; osteoclastoma; myeloid sarcoma; myeloma.)

S. PATH.

This is one of the most striking of bone tumours, and its clinical and pathological features are uniform and characteristic. Unfortunately the terminology is complicated and misleading. Since the tumour does not infiltrate except to a very limited extent, and only gives rise to metastases in exceptional cases, it is fitting that the old name *myeloid sarcoma* should be discarded. The term *myeloma* should also be abandoned, for it is almost certain that the tumour does not arise from bone marrow, and moreover "myeloma" leads to confusion with "multiple myelomata," an entirely distinct form of neoplasm.



FIG. 69. Giant-cell tumour of bone, arising at the proximal metaphysis of the humerus. The tumour has expanded the bone and forms an ovoid mass, partly solid and partly cystic.

(By courtesy of Mr. J. W. Struthers)

believed that the tumour originated in bone marrow and he regarded the giant cells as modified myeloplaxes or megakaryocytes. At the present time, however, it is generally thought that the giant cells are derived from osteoclasts, the foreign-body giant cells normally engaged in bone resorption.

The giant-cell tumour of bone occurs in either sex and at any age, but generally it is found between the ages of fifteen and thirty years. In a large proportion of cases the tumour arises in a bone of the lower extremity. Like bone sarcoma it is situated most frequently close to the knee, especially at the distal end of the femur. Any long bone, however, may be affected, and giant-cell tumours have been found in the bones

The origin of the giant-cell tumour of bone has been a subject of controversy since the time of Nélaton, who was the first to describe it adequately. Nélaton

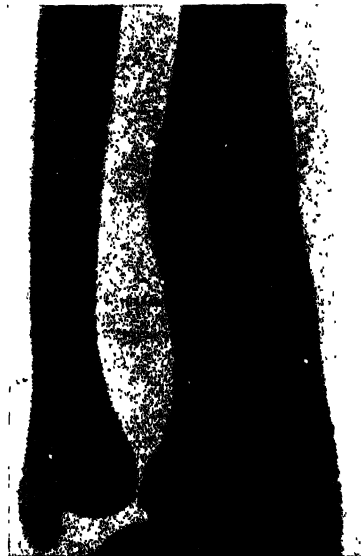


FIG. 70. Radiogram of a giant-cell tumour at the distal end of the radius. The tumour is situated close to the metaphysis and has expanded the bone. The lobular character is clearly seen.

of the upper limb, in the scapula and the bones of the pelvic girdle. It is found in such situations as the distal end of the radius, tibia or fibula, relatively rare sites of sarcoma. It is not uncommon in the jaws.

The tumour originates either in the metaphysis or in the epiphysis, where it forms a localized, well demarcated growth, often more or less globular in shape. It may grow eccentrically, and reach the surface of the bone on one aspect only, or it may enlarge concentrically. Unlike a sarcoma, it is sometimes not restrained by the epiphysial cartilage, and may spread as far as the articular cartilage. Penetration of the joint is exceptional.

The tumour is composed of soft, cellular, very friable and often jelly-like tissue, which is usually very vascular, and from hæmorrhage may be of a dark reddish purple or maroon colour, and aptly likened to

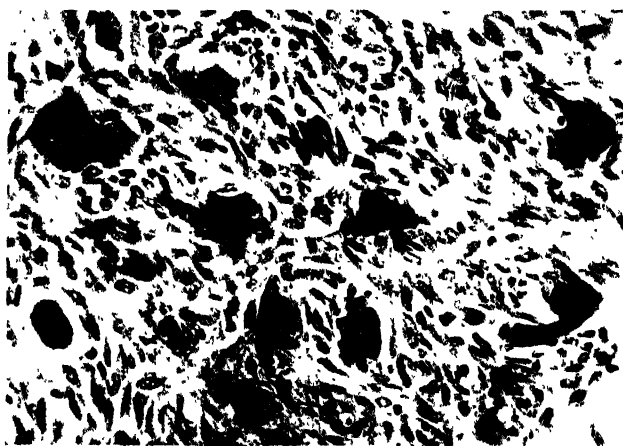


FIG. 71. Giant-cell tumour of bone. $\times 300$. Note the giant cells of characteristic appearance, and the stroma of small spindle-shaped cells.

(Laboratory of Royal College of Physicians of Edinburgh.)

red currant jelly. The tumour is traversed by delicate fibrous or bony trabeculae, which in radiograms give a characteristic honeycomb or mosaic appearance. The central portions frequently undergo cystic degeneration, and occasionally one large cyst replaces the greater part or even the whole of the tumour.

The soft tissues are invaded only in exceptional cases, and the tumour usually remains surrounded by a thin shell of bone. Even when a tumour has attained large size there still remains a thin covering of new bone beneath the periosteum—a complementary process of bone resorption and replacement which is loosely termed “expansion.”

Although the above description applies to the vast majority of these tumours, a few examples have been described, principally at the distal end of the radius, which differ in being relatively avascular—so-called “white” giant-cell tumours.

Microscopically, the tumour consists principally of a spindle-cell stroma in which are scattered giant cells of characteristic appearance.

The giant cells vary in number in different tumours and in different parts of the same tumour, but their appearance is remarkably uniform, and is identical with that of foreign-body giant cells. They contain numerous nuclei and an abundant homogeneous cytoplasm. The nuclei usually number from 10 to 20, but as many as 100 may be present. They lie principally in the central part of the cell, and are sometimes arranged like a rosette. Each nucleus is distinct from its fellows and of uniform appearance—small, rounded or oval, and intensely basophilic.

The stroma may be fibrous or cellular, the latter being to some extent an indication of rapid growth. The cells are small and principally spindle-shaped. Mitotic figures are rare. Occasionally scattered through the stroma are collections of large clear "foamy" cells, containing an abundance of doubly refractile lipoid material—a form of xanthoma. The blood vessels are numerous, large and thin walled.

Progress and Effects of Giant-cell Tumours. Giant-cell tumours usually progress slowly, and for a considerable time may cause little disability. Often the tumour remains unrecognized until a fracture occurs, a fairly frequent complication. In other cases, weakening or even collapse of an adjacent joint may occur from penetration of the epiphysis. Rarely the growth of the tumour appears to be arrested spontaneously, and sometimes from central liquefaction the whole mass becomes converted into a single large bone cyst, in the fibrous walls of which only small traces of the original tumour are still to be found.

Malignant change may occur, though not commonly. The frequency of this complication is a matter of great practical importance to the surgeon, who is faced with the necessity for deciding between amputation and local attack upon the tumour. There is no doubt that in rare cases the tumour is actually malignant, for a few authentic cases have been reported in which pulmonary metastases developed, and it is equally certain that occasionally the tumour undergoes sarcomatous transformation after an early simple course, and gives rise to round-cell or spindle-cell metastases. In the great majority of cases, however, the tumour is essentially non-malignant, and there is thus ample pathological evidence to warrant the conservative measures in vogue at present.

MALIGNANT TUMOURS OF BONE

Since the days when all soft tumours of bone were thought to be cancers there have been many changes in their nomenclature and classification. The first important advance was the segregation of secondary tumours, and later the recognition of the various types of primary tumours. In recent years our knowledge of this latter group has been greatly increased and clarified by the work of those connected with the Registry of Bone Sarcoma in the United States of America, and for the first time accurate information has become available upon many aspects, clinical and pathological, of a large series of cases. According to the Registry classification, the malignant primary tumours of bone may be divided into the following principal varieties:—

- (1) True bone sarcoma (osteo-sarcoma: osteogenic sarcoma),

including periosteal sarcoma, central sarcoma, sclerosing sarcoma and telangiectatic sarcoma.

- (2) Tumours of bone marrow—multiple myeloma.
- (3) A tumour of doubtful nature—endothelial sarcoma or Ewing's tumour.
- (4) A group of uncommon and unclassified tumours.

Bone Sarcoma (Osteo-sarcoma ; Osteogenic sarcoma)

This is the commonest of the primary malignant tumours of bone, and it is said to account for 30% of all sarcomata. It affects males somewhat more often than females, and it occurs with overwhelming frequency in the second decade, the period of most active skeletal growth. In patients over fifty years of age it is very uncommon, except as a complication of some dystrophy such as osteitis deformans. In its pathological aspects the disease is one of great complexity, but its clinical features and end results are only too uniform, for, with very few exceptions, its malignancy is extreme, and even after early radical treatment a fatal issue is not long delayed.

Bone sarcoma usually arises in or near that part of the bone in which proliferative changes normally progress most actively, namely, the metaphysis. Not infrequently, moreover, it supervenes upon other bone diseases, such as osteitis fibrosa or osteitis deformans (the last named alone accounting for about 5%), and it is significant that all these diseases are characterized by profound disturbance of the processes of bone growth and repair. In some cases trauma appears to determine the onset of the tumour.

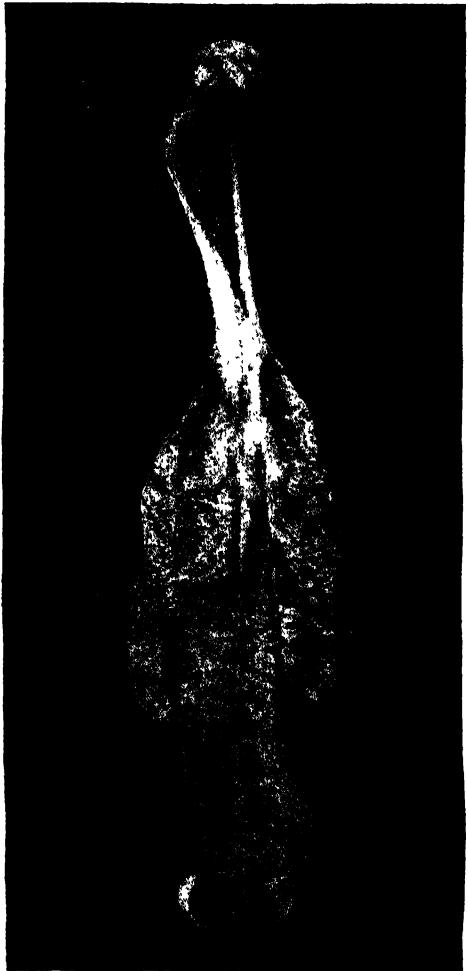


FIG. 72. Sarcoma of the femur in a young person. The tumour appears to have originated near the distal metaphysis, and has extended far, both along the marrow cavity and under the periosteum. Note that it has not penetrated the epiphysal cartilage nor involved the joint.

(Department of Surgery, University of Edinburgh.)

Bone sarcoma is generally regarded as arising from bone-forming cells (osteoblasts), but it is not necessarily composed of bone, for bone formation is only a potential property of these cells, and when malignant they revert more closely towards the embryonic state and lose their bone-forming habit. In some tumours this reversion is almost complete and the cells produce only a delicate mesenchymal stroma, and the tumour remains soft and fleshy; or they may differentiate in greater or less degree and produce mucoid material, cartilage, or bone.

To emphasize this supposed origin of the tumour from bone-forming cells or their non-bone-forming derivatives, Ewing has suggested the title *osteogenic sarcoma*, and this name has obtained wide acceptance, particularly in America. The term is, however, unfortunate in this sense—that it is often interpreted as “bone producing,” the antithesis of its intended meaning.

Types of Bone Sarcoma.

Classifications of bone sarcoma are clumsy and confused, and very perplexing to the student. Fortunately the general trend at present is towards simplification, and this has been assisted by the work of the American Registry. The following principal types may be recognized:—

(1) *Periosteal Sarcoma.* This is the commonest type. The greater part of the tumour lies deep to the periosteum, and raises it off the bone cortex, but the tumour also infiltrates the substance of the bone and may extend along the medullary cavity. In some cases the tumour appears to arise from the periosteum; in others it is probably derived from the connective tissues continuous with the periosteum that penetrate the bone and line the bone spaces.

(2) *Medullary or Central Sarcoma (Endosteal Sarcoma).* Tumours situated within the bone, and not extending to the surface,

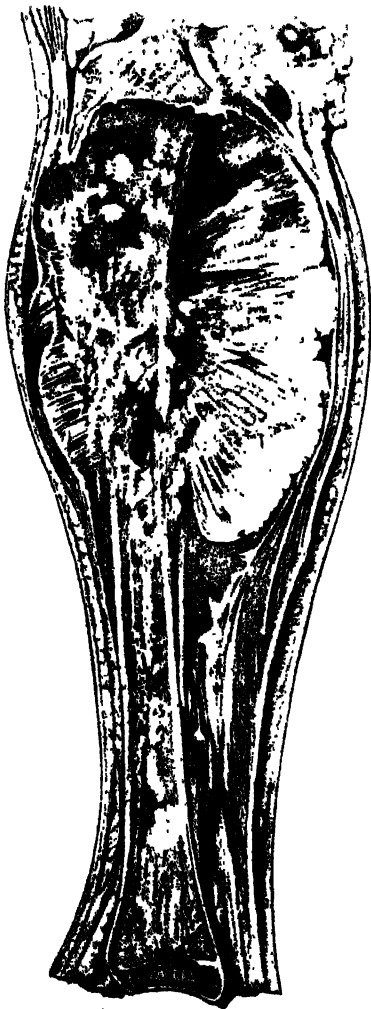


FIG. 73. A bone sarcoma arising at the proximal metaphysis of the tibia. The tumour has infiltrated the marrow cavity and has elevated the periosteum. Proximally it is limited by the epiphysal cartilage. Note the radiate spicules of new bone formed in the tumour.

(Museum of Royal College of Surgeons of Edinburgh.)

figure largely in older surgical descriptions, but modern experience shows that sarcoma of this class is rare.

(8) *Sclerosing or Ossifying Sarcoma*. This type is characterized by the formation of a large amount of new bone in the tumour. In some cases the tumour is extensively ossified, even to the hardness of ivory. The new bone formation is generally looked upon as evidence of some kind of defensive reaction on the part of the tissues, but there is little proof that a sclerosing sarcoma is any less malignant than other varieties.

(4) *Telangiectatic Sarcoma (Malignant Bone Aneurysm)*. In some bone sarcomata the vascularity is so great that the greater part of the tumour is occupied by blood vessels, which are large and extremely



FIG. 74. Bone sarcoma. $\times 275$. A spindle-cell sarcoma of the tibia, The tumour is highly cellular. It is composed of elongated, spindle-shaped cells, some of which have been cut transversely and consequently appear to be rounded.

(Laboratory of Royal College of Physicians of Edinburgh.)

thin-walled. Sometimes, indeed, the blood vessels have no complete endothelial lining, but are mere spaces surrounded by the malignant tumour cells. The vascularity may be such that the tumour pulsates. Since the tumour cells have ready access to the blood stream the risk of early metastases is very great, and the outlook is correspondingly grave. This type of tumour is especially apt to affect young subjects.

Morbid Anatomy. The ends of the long bones of the extremities are affected with greatest frequency, but such irregular bones as the jaws, the scapula and the bones of the pelvic girdle are by no means exempt. It is estimated that the bones of the lower limb are involved in about 70% of cases, the distal end of the femur and the proximal end of the tibia being most frequently affected. In the upper limb the proximal end of the humerus is the site of election. The regions of the wrist and ankle joints are very rarely involved (compare giant-

cell tumour), and sarcoma of the smaller bones of the hands and feet is exceptional.

In a typical example of a sarcoma near the end of a long bone the growth extends widely along the paths of least resistance, permeating the interstices of the bone and eroding its lamellæ. It extends along the marrow cavity, permeates the cortex and erupts on the surface. The periosteum for a time resists invasion and becomes raised from the surface of the bone, and deep to it the tumour spreads widely so that eventually it may form a fusiform mass ensheathing the bone extensively.

Often the tumour consists of two main portions, an elongated, ill-



FIG. 75. Bone sarcoma. A spindle-cell sarcoma of the femur. Note the large blood space on the left. It is thin walled, and in places it lacks even an endothelial lining and is in direct contact with the malignant cells.

(Department of Surgery, University of Edinburgh.)

defined mass permeating the marrow cavity and an ensheathing growth under the elevated periosteum, the two portions being separated in much of their extent by the more resistant cortical bone. If with further progress the tumour perforates the periosteum, it extends widely within the soft tissues, causing great swelling and œdema with dilatation of the superficial veins. The skin becomes tense and glossy, but for a long time it resists actual invasion and ulceration. The epiphysis is rarely invaded, and since the periosteum is attached to the circumference of the epiphysial cartilage the joint is not affected until late.

The appearance of the tumour varies greatly. Most often it is soft, red, fleshy and very vascular, with areas of hæmorrhage and necrosis. In other cases the appearance is modified by the presence of cartilage or of bone. Cartilage renders the tumour more firm, with bluish translucent areas (chondrosarcoma, *see* p. 170). Bone of new formation is usually present in greater or less amount. When new bone

predominates the marrow cavity may be obliterated and the whole end of the diaphysis be increased in circumference by a fusiform mass of bone, which sometimes assumes ivory-like hardness. This is called the sclerosing type.

Microscopic Appearances. The microscopic features of bone sarcoma are complex. The tumour cells show great diversity and the picture is complicated by such secondary processes as bone resorption or new bone formation.

The predominating type of cell is small and spindle-shaped, but large, polyhedral and even round cells may occur. The cells are hyperchromatic and with frequent mitoses, often of irregular type. Giant cells of the "malignant giant-cell" type are often present. Cells of this type have a characteristic appearance, very different from the cells of the so-called *giant-cell tumours*; they are irregular in shape and size, and contain few nuclei which are oval or indented, joined together, and deeply hyperchromatic.

One of the most conspicuous features is the structure of the blood vessels. They are large and thin-walled and in close relation to the tumour. In places even an endothelial lining is lacking, and the blood flows in large clefts lined by tumour cells; consequently there is a great liability to liberation of malignant emboli.

Ossification in Bone Sarcoma. The production of new bone is a characteristic feature of nearly all cases of bone sarcoma. The new bone is laid down principally under the periosteum. In some cases there are radiating spicules developed like stalagmites perpendicular to the surface of the bone. Such new formations have a characteristic "sun-ray" appearance in radiograms. The disposition of the spicules appears to depend upon the arrangement of smaller vessels extending perpendicularly from the elevated periosteum into the cortex. Less often the new bone takes the form of a small wedge-shaped ossification which occurs where the periosteum is elevated beyond the advancing edge of the tumour.

Metastases in Bone Sarcoma. Metastatic deposits are of extremely common occurrence, hence the almost uniformly bad prognosis. Owing to the intimate relationship of the vessels to the tumour, blood-borne emboli are common, and the lung is the most frequent site of their arrest. Less commonly, or in the later stages, other viscera and other bones may be affected. It would appear that the metastases occur

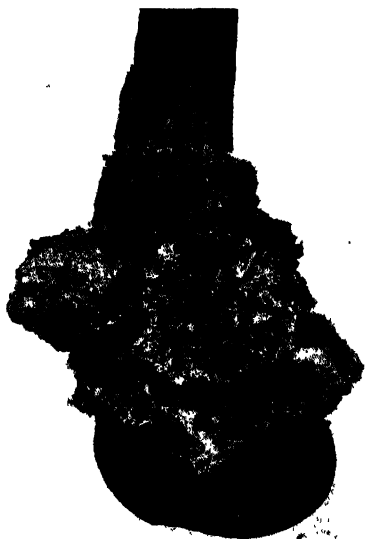


FIG. 76. Bone sarcoma arising at the distal metaphysis of the femur. Macerated specimen which shows much new bone laid down as spicules perpendicular to the surface of the femur.

(Museum of Royal College of Surgeons of Edinburgh.)

early, but may grow slowly. They are probably often present at the time of operation, but only after a period of months do they give rise to any clinical signs. Microscopically, the metastases tend to reproduce the varied structure of the original growth, and they may



FIG. 77. Bone sarcoma of telangiectatic variety. The bone trabeculae have undergone resorption, and the intervening spaces are occupied by tumour cells. Note the large number of osteoclast giant cells which lie in apposition to the bone trabeculae.

contain fibrous matrix, and cartilage, but it is remarkable that metastases in soft tissues such as the lungs rarely produce bone.

Chondrosarcoma

(Chondrifying sarcoma ; sarcomatous chondroma.)

Strictly speaking, the term chondrosarcoma should be restricted to simple chondroma which has undergone malignant change, but in practice it is understood to include any sarcomatous tumour containing cartilage in excess. The majority occur in relation to the ends of long bones, forming bulky lobulated masses which on naked-eye inspection resemble simple chondromata, but microscopically show also sarcomatous elements in varying proportion. This type of tumour is now generally regarded as a bone sarcoma with a predominance of cartilage matrix rather than as a specific type.

In their malignancy and course these tumours vary greatly. They are particularly insensitive to irradiation. A peculiar feature is a tendency to extend along the lumen of blood vessels, and such a growth has been known even to reach the heart. Multiple secondary growths are frequent, but sometimes a solitary metastasis appears and attains considerable size before the disease becomes generalized.



FIG. 78. Chondrosarcoma of the femur. The shaft of the femur is permeated by solid tumour tissue. The outer parts of the tumour are composed of lobules of jelly-like material separated by fibrous trabeculae.

(By courtesy of Mr. J. W. Struthers.)

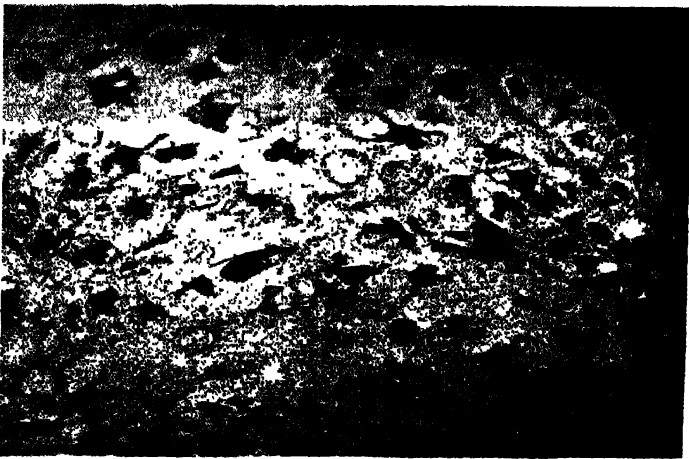
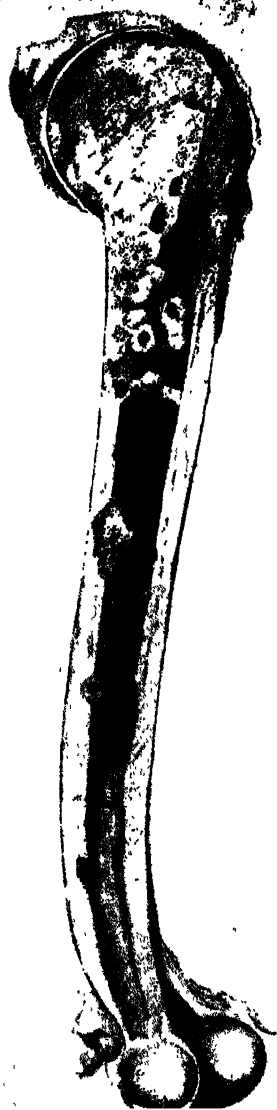


FIG. 79. Chondrosarcoma undergoing mucoid change. Many of the cells are distended to signet-ring shape by large globules of mucoid material, and the intercellular substance is infiltrated by a similar material.

(Department of Surgery, University of Edinburgh.)

Multiple Myeloma (Plasmacytoma)

This rare disease is characterized by the development of multiple tumours in many parts of the skeleton. It is a disease of adult life, occurring usually between the ages of forty and sixty, and commonly in men. Any part of the skeleton may be involved, but the tumours are usually most evident in the sternum, the ribs, the vertebræ, the skull and the femora.



The tumours are usually small, but occasionally they may grow to the size of walnuts and a few attain even greater dimensions. They invade any part of the bones, but mainly the marrow cavity, and form rounded or oval well-circumscribed masses of grey or greyish-red colour and of soft consistency. Adjacent bone is invaded by the tumour and is decalcified, without any new bone formation, so that when the bone is extensively affected the condition may bear a superficial resemblance to osteitis fibrosa or to metastatic carcinomatosis. The bone may be so thinned that fracture results, and in the later stages the tumours invade the surrounding soft parts. The growth of a tumour in the vertebral column commonly leads to severe pain and eventually may cause compression paraplegia. In the later stages of the disease there is a considerable degree of anæmia, doubtless resulting from destruction of the red marrow.

A well-known feature of the disease, which only occurs, however, in from 50% to 70% of cases, is the excretion of proteose in the urine (Bence-Jones). The proteose, which may appear in enormous amount, gives the ordinary reactions for this class of substance, and is recognized by its behaviour when heated. At a temperature of about 55° C. the urine becomes opaque, and a sticky coagulum forms on the surface. On heating further, to the neighbourhood of 85° C., it disappears, but forms again when the urine cools. Proteosuria was formerly regarded as pathognomonic of myelomatosis, but it is now recognized that it occurs also, though in small amount, in certain cases of leukaemia, in secondary tumours of the skeleton, and occasionally in nephritis.

FIG. 80. Multiple myelomata. Numerous small rounded tumours occupy the head and shaft of the humerus.

(Department of Pathology University of Edinburgh.)

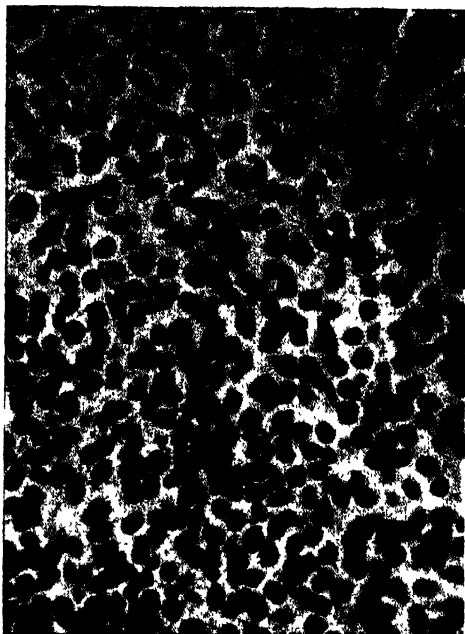


FIG. 81. Plasmacytoma (multiple myeloma). The tumour contains many plasmacytes, large oval cells of which the nucleus lies eccentric and has a coarse meshwork of chromatin.
(*Department of Pathology, University of Glasgow*)

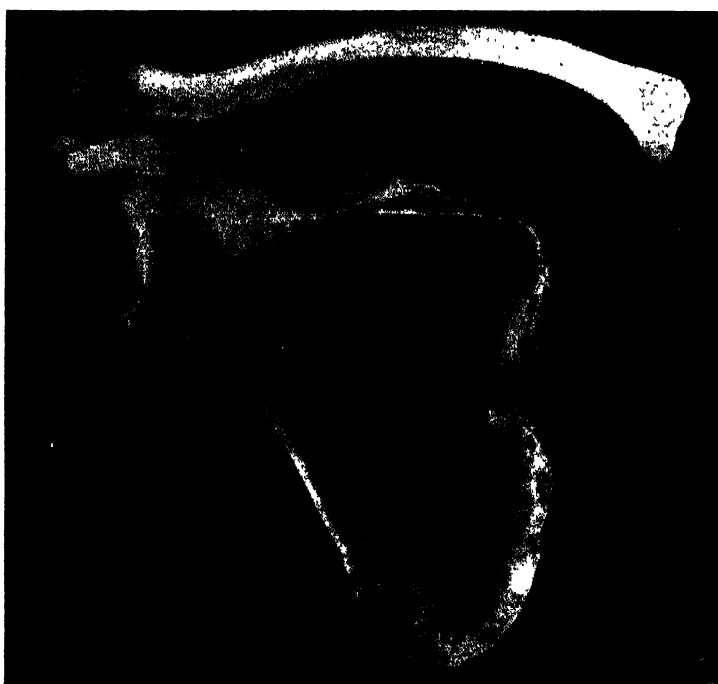


FIG. 82. Multiple myeloma of scapula and clavicle. Radiograph of specimen.
(*Department of Pathology, University of Glasgow.*)

Microscopically, the growths are composed of diffusely arranged round cells with little or no intercellular substance. Usually the cells are of the plasma-cell type, with deeply basophil cytoplasm and a small eccentric nucleus, but sometimes cells of lymphocyte type, or cells resembling the primitive white cells or myelocytes, may preponderate. In exceptional cases erythroblasts have been described. The condition is generally regarded as a disease of the blood-forming tissues rather than of bone, and the cells are believed to originate in the bone marrow. It is true that plasma cells do not occur in this situation under normal circumstances, but they are presumed to be related to the other more definitely hæmatopoietic cells. In this connexion it is interesting to note that the spleen is usually enlarged, as in leukæmia and lymphadenoma, and that visceral metastases occur in the liver and the spleen and occasionally in the lymph glands, but not in the lungs.

Solitary Plasmacytoma. In rare instances, especially in middle age, a plasmacytoma may be single and without other bony changes. It is a simple tumour and frequently comes to notice as a result of a pathological fracture of one of the limb bones, rarely a vertebra. The tumour occurs centrally in any part of the shaft of the bone, which shows rarefying osteitis. The tumour is amenable to surgical or radiotherapeutic treatment, especially the latter.

Endothelial Sarcoma. (Ewing's Tumour)

This tumour has only been recognized as a distinct type in recent years, and it seems possible that most bone tumours hitherto called small-round-cell sarcoma belong to this type. Since Ewing first described it a number of cases have been recorded, chiefly in America, and according to the figures of the Registry of Bone Sarcoma it is not uncommon; its occurrence is variously estimated at from 7% to 10% of all primary malignant tumours of bone. It is commonest in young persons, particularly between the ages of five and fifteen, and it is three times commoner in males than in females. A history of recent injury is often obtained. The long bones, the tibia, humerus and femur, are those most frequently affected, but the tumour may occur in the short bones of the extremities, particularly in the calcaneus.

The tumour differs from other varieties of sarcoma in that it arises usually from the mid-part of the diaphysis of the bone. It arises in the bone marrow, and spreads in all directions from its point of origin, penetrating the bony lamellæ to reach the surface of the bone. The periosteum at first resists invasion, and layer after layer of new bone is formed and subsequently eroded.

The appearance of the tumour is remarkable, for it is soft, greyish-white in colour and somewhat brain-like, often with semi-liquefied areas of degeneration which may resemble pus. When such material is seen lying between partly eroded bone lamellæ the appearance suggests osteomyelitis, for which it is often mistaken.

The first symptom is usually pain, and this is often intermit-

tent, recurring in attacks of increasing severity over a period of weeks or months. The swelling appears later and may vary in size, retrogression being accompanied by temporary relief of symptoms. Pathological fracture may occur, but is not very common. There is often a slight leucocytosis and secondary anaemia. The tumour responds well to radiation, and by suitable treatment its growth and spread may be controlled for a considerable period. Finally, however, metastases appear in other bones and in lymph glands and viscera, and the disease eventually proves fatal.

The microscopic appearance is noteworthy for its simplicity and uniformity, contrasting greatly with the pleomorphism of other sarcomata of bone. The tumour is composed entirely of small rounded or polyhedral cells, arranged in coherent sheets with little or no intercellular substance. Sometimes the masses of cells are embedded in a delicate connective tissue framework, but often this is lacking. From degeneration of the portions furthest from their source of nourishment a perivascular grouping of the surviving cells often results. Mitotic figures are numerous.

The origin of Ewing's tumour is not clear. Most authorities

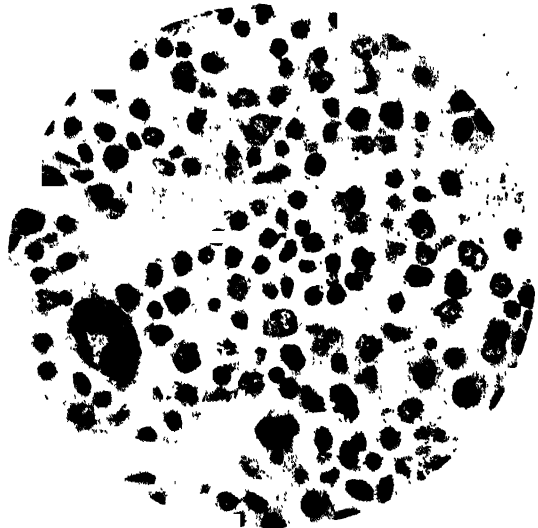


FIG. 83. Multiple myeloma. $\times 450$. The greater number of the tumour cells are myeloblasts -- primitive white blood cells -- in addition to a few giant cells.

(Laboratory of Royal College of Physicians of Edinburgh)

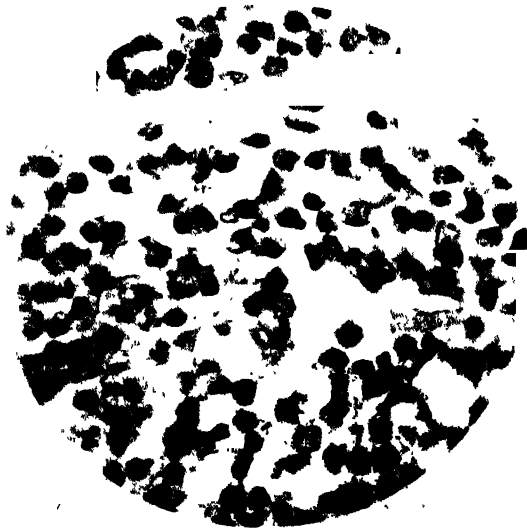


FIG. 84. Ewing's tumour. The tumour is composed of polyhedral cells with little intercellular material.

(Laboratory of Royal College of Physicians of Edinburgh)

regard it as derived from the perivascular endothelial cells of the marrow. Recent work suggests that many supposed cases of Ewing's tumour have actually been examples of metastatic growths, secondary to bronchial carcinoma or to neuroblastoma of the adrenal gland.

Endothelioma of Bone

Until recent years "endothelioma" was the graveyard of unclassifiable tumours, but since the adoption of stricter histological standards for endothelial cells these tumours are now acknowledged to be rare. Endotheliomata of bone described in recent years have resembled bone sarcoma, both in the clinical course and in their pathological aspects, the diagnosis being made only by microscopic sections, in which cells of endothelial type are seen apparently arising from the internal coat of vessels, and forming alveoli or tubules, which in some cases contain blood.

Parosteal Fibrosarcoma

This tumour also appears to be rare, but it is of interest in that it is believed to account for a certain proportion of the "cures" of bone sarcoma, the malignancy being relatively low and the prognosis correspondingly good. Strictly, it is not a bone tumour, but arises on the outer aspect of the periosteum, and forms a fairly well encapsuled mass in the soft tissues, and leads to little or no erosion of the bone. Microscopically, it resembles a cellular fibroma, and is composed of elongated cells embedded in a scanty fibrous stroma. Since the tumour adheres to the periosteum it appears on clinical examination to be fixed to the bone, and it may spread to some extent around the bone as a sheath. Invasion of the surrounding parts is a late occurrence, as are metastases, and the outcome of radical excision is therefore promising.

SECONDARY TUMOURS IN BONE

Bone is a common site for secondary tumours derived from various types of primary growths. Such secondary tumours may arise (1) by local extension of the primary growth, or (2) by dissemination of cells along the lymph or blood vessels.

(1) Involvement of a bone by the direct extension of a malignant tumour is a familiar occurrence. It is observed when a carcinoma of the tongue or the floor of the mouth invades the mandible; when a rodent ulcer or lupus-carcinoma of the face destroys the bones of the skull (Fig. 85); or when a carcinoma that has arisen in a chronic leg ulcer invades the tibia.

In bones thus involved decalcification and destruction are the most outstanding changes and are aggravated by superimposed infection. As in other conditions in which hyperæmia affects bone, a gradual process of decalcification occurs and the bone becomes softened and replaced by the extending tumour, so that in a macerated specimen it has a worm-eaten or sand-papered appearance. Usually no new

bone is formed at the extending margin of the tumour or within the tumour itself, unless the invading tumour is one of great vascularity, when bone resorption and new bone formation may occur simultaneously. In such instances the new bone is represented by light spicules of feathery appearance that project into the tumour from the surface of the bone on which it impinges.

(2) Involvement of bone by malignant cells disseminated from a distant growth occurs most commonly in cancer of the breast, prostate and bronchus, less often in cancer of the kidney, and in the late stages



FIG. 85. Destruction of the facial bones as a result of invasion by lupus-carcinoma.

(Museum of Royal College of Surgeons of Edinburgh.)

of many other types of cancer. Malignant tumours of the thyroid gland commonly metastasize to bone, but this growth is somewhat of a rarity.

Certain bones are especially liable to be the seat of metastatic growths. The ribs, vertebræ, sternum, skull, pelvic bones, femur, and humerus are commonly affected, and less often the mandible, scapula and clavicle. The distal bones of the extremities are rarely involved.

Evidence is overwhelming in favour of the view that most metastatic bone tumours result from blood-borne emboli of malignant cells. Such cells derived from any source other than a primary tumour of the lung must be presumed to have passed through the pulmonary circulation before reaching the systemic circulation, and the possibility of this

occurrence is well recognized. The work of Schmidt is of great importance in showing how malignant emboli may behave on reaching the lungs, for it has shown that the cancer cells may grow directly from the pulmonary arterioles into the capillaries and veins without invading the vessel walls. In this way metastases may be disseminated by the systemic circulation, yet leave no trace in the lungs.)

It has been claimed that in some cases metastatic bone tumours result from permeation of the lymph vessels by malignant cells, but the evidence for this view is somewhat slender, for lymph channels have not been demonstrated in the bone marrow, and the lymph vessels of the cortex do not extend beyond the endosteum. Moreover, bone metastases begin centrally, and often at a very considerable distance from the primary growth, and it is rarely possible to demonstrate



FIG. 86. Metastatic growths in the bones of the skull. The primary tumour was a cancer of the stomach. The metastases have led to decalcification and erosion of the bones. No new bone has been formed.

(Museum of Royal College of Surgeons of Edinburgh.)

involvement of intermediate lymph channels. (See also chapter on Diseases of the Breast.)

The principal evidence in favour of lymph spread to bone is the special liability of certain bones to metastatic growths and the comparative immunity of other bones; but Pincy has advanced a reasonable explanation for this "selectivity," which accords well with the theory of hæmatogenous spread. He points out that the sites mentioned above are precisely those where red bone-marrow persists in adult life, and that the sinusoidal character of the circulation in the red marrow, by its almost stagnant condition, favours the lodgment and proliferation of cancerous emboli. When a metastatic growth is found at sites where red bone marrow is not present normally, for example, in the shaft of the tibia or in the small bones of the hand, it has been suggested that the constitutional effects of the malignant disease, *e.g.*, secondary anæmia, have been such as to stimulate an erythroblastic reaction in the marrow, which would afford a favourable site for the growth of cancer cells.

The blood changes are often characteristic. There is usually

hypochromatic anæmia, and the red cells and leucocytes are of immature type. There is a low platelet count. The degree of anæmia does not bear a definite ratio to the extent of the metastasis.

The Changes in the Bones. The effects of metastatic tumours upon the bone are characterized principally by decalcification and destruction. When small, a metastatic tumour appears as an opaque, greyish focus in the interior of the affected bone, and causes no striking change in it; but as the tumour grows the adjacent bone becomes encroached upon and rarefaction occurs for some distance around. With the exception of metastases from carcinoma of the prostate, new bone is formed only in rare instances. A localized spherical or ovoid expansion of the bone occurs, but this enlargement is rarely very considerable. A thin shell of bone usually circumscribes the tumour and the periosteum remains intact. If the affected bone is submitted to undue strain, fracture readily occurs. In the spinal column several vertebræ may collapse, resulting in the development of kyphosis, and/or pressure on the cord or on the spinal nerves. At the site of fracture there may be a considerable attempt at repair by new bone formation, but firm union is very rarely attained.

Other characteristic features of bone metastases vary according to the situation and nature of the primary growth.

Cancer of the breast, from its relative frequency, is the most common source of the metastases. The vertebræ, ribs, and sternum are most often affected, but not infrequently deposits may be found in the upper end of the femur and of the humerus. In a few instances almost all the skeleton is affected, producing the condition sometimes known as "generalized cancerous osteomalacia." Frequently osseous metastases appear months or many years after removal of the diseased breast.

In cancer of the thyroid



FIG. 87. Thyroid metastasis in bone. A secondary growth in the humerus from an adenocarcinoma of the thyroid. The tumour has destroyed the distal half of the bone and has elevated the periosteum. At the centre, the tumour has undergone necrosis.

(Museum of Royal College of Surgeons of Edinburgh.)

gland the skeleton is one of the commonest sites for metastases. They are found most often in the vertebræ, skull, and sternum, but they may occur also in the long bones of the extremities. The primary growth, which is not infrequently a malignant adenoma, may be so small as to escape detection, and the thyroid gland then appears normal on clinical examination. The metastases are rarely numerous, and may be single, therefore in some instances their removal may be undertaken with a favourable prospect of cure.



FIG. 88. Secondary tumour in bone. Metastasis, at the distal end of the femur, from an adenocarcinoma of the kidney. The tumour is highly vascular, and as a consequence the bone has undergone extensive decalcification.

(Department of Surgery, University of Edinburgh.)



FIG. 89. Secondary tumour in bone. Radiogram. (From same specimen depicted in Fig. 88.)

The histological appearance of the secondary tumours is very variable. They may resemble the primary thyroid growth, they may look like normal thyroid tissue, or they may show any degree of malignancy. The secondary tumour may produce thyroid secretion, and its removal has been known to be followed by myxœdema.

Hypernephroma of the kidney is sometimes associated with secondary growths in bones. Usually the metastasis is single and may not be manifest until a considerable time after removal of the renal tumour,

and in a few instances the source of metastasis is only revealed after thorough examination or at autopsy. Favourite sites for metastases are the upper end of the femur, the sternum, and the pelvic bones. New bone formation within the tumour is often a prominent feature.

Carcinoma of the prostate is often associated with skeletal metastases. It is important to recognize that no prostatic enlargement may be detected on rectal examination, and in a few instances not until the prostate has been examined histologically can its malignant nature be established. Irradiation by X-rays or radium of a malignant prostate has sometimes appeared to precipitate the appearance of osseous metastases. The secondary growths are generally disseminated widely,



FIG. 90. Vertebral metastasis of a papillary adenocarcinoma of the kidney. Columnar epithelial cells arranged in papillary formation are invading the bone.

(Laboratory of Royal College of Physicians of Edinburgh.)

but the pelvic bones, the spine and the skull are the commonest sites.

In many instances the disseminated cancer cells excite a remarkable osteoplastic reaction which results in both increase in density and girth of the affected bone. The medullary canal is often obliterated, and a severe degree of secondary anæmia may result from destruction of the bone marrow.

It has been shown that in metastasizing carcinoma of the prostate the serum "acid" phosphatase is increased; and it has been suggested that its estimation may be helpful in diagnosis. Elevation to from 6 to 10 units is supposed to be very suggestive. The source of the increased serum phosphatase is probably the carcinomatous tissue. In the normal prostate the "acid" phosphatase is a product of the acinar epithelium, a capacity which is apparently retained when malignant change supervenes.

On a number of occasions it has been observed that the skeletal metastases of carcinoma of the prostate may show retrogression or may

even disappear following castration. Stilboestrol in massive doses may have a similar effect, though it is inconstant.

TUBERCULOSIS OF BONES AND JOINTS

Tuberculosis of bones and joints occurs with greatest frequency in childhood, especially during the first six years of life, and only in a small proportion of cases does it begin after the age of fifteen. Adults are not immune however, and the disease may occur even in old age. In children the process is often slow and tractable, but in adults resistance is often poor, so that the progress can be checked only by radical measures.

Bone tuberculosis and joint tuberculosis are so often combined that it is appropriate to consider them together, although in some situations, *e.g.*, in the vertebræ, skull, and bones of the hands and feet, the disease is confined to bone.

It has never been clearly settled whether tuberculous arthritis follows disease of one of the bones or arises as a direct infection of the joint. Perhaps most observers believe that in the majority the bone is affected first, the joint later. Joint disease spreads more rapidly and causes more obvious effects than the earlier and less conspicuous bone lesion. This view is generally accepted for the majority, but it is

beyond doubt that the disease sometimes affects the synovial membrane only.

In either case the disease is always secondary to tuberculosis elsewhere, and the infection is blood-borne from a focus in lymph glands or the lungs. (One outstanding exception to this rule is tuberculosis of the temporal bone, which is usually secondary to middle-ear disease, a contact infection.)

The infecting organism may be of human or bovine type, and the relative frequency with which one or the other type is responsible is said to vary in different countries. In Scotland, ac-

ording to Griffith, the bovine organism is present in 42·8% of cases, whereas in England the corresponding figure is 18% (*see p. 85*).

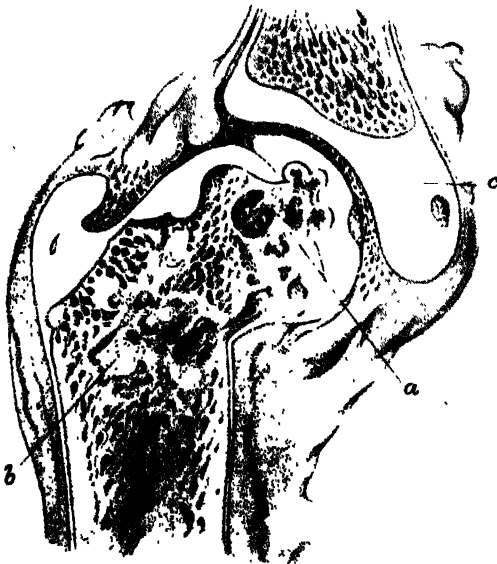


FIG. 91. Tuberculosis of the femur in a child aged two years. (a) Tuberculous granulation tissue of gelatinous appearance, (b) an area of caseation, (c) the acetabulum. The disease has originated at the metaphysis and has spread thence into the epiphysis and also down the shaft.

The Sites Affected. In long bones the disease usually begins in the epiphysis, rarely in the metaphysis. In the short long bones of the hand and feet, on account of their arborescing blood supply, the disease begins in the diaphysis. Subperiosteal tuberculosis is not infrequent in adults, but is rare in children.

The relation of the synovial membrane to the articular end of the bone is an important factor in determining spread of the disease. When the capsule extends beyond the epiphysal cartilage, as, for example, at the hip joint, the metaphysis comes into direct relationship with the synovial membrane, and consequently the joint is infected directly.

The liability to tuberculosis is not shared equally by all bones and joints. Some are particularly susceptible, others are involved only rarely. *In children*, the vertebræ and the joints of the lower limbs are affected in a large proportion of cases (60% to 80%), in the following order of frequency: vertebræ, hip, knee, ankle. The temporal bone is a common site, by direct spread from middle-ear infection, but tuberculosis in other cranial bones is extremely rare. The tibia and ulna are occasionally involved apart from joint lesions. Not uncommonly two foci are present, *e.g.*, at the hip and spine, or there may be lesions elsewhere, especially in the kidney. *In adults* the joints of the upper extremity are more liable to infection, in the order, shoulder, elbow, wrist. The knee is also a common site.

The special susceptibility in childhood, and the predilection of the disease for certain bones and joints are attributed to such factors as growth activity and exposure to injury. Growing bones appear to be more susceptible than the mature. The frequent involvement of the bones and joints of the lower extremity and of the spine is attributed to the strain to which they are exposed.

Pathology of Bone Tuberculosis

When a bone is invaded by tubercle bacilli the effects differ in no particular from those of tuberculosis elsewhere, they are conditioned merely by the structural characteristics of osseous tissue. There is the usual evolution of tuberculous granulation tissue, so that the bone at and around the diseased area undergoes slow but progressive decalcification, hence the "osteoporosis" which

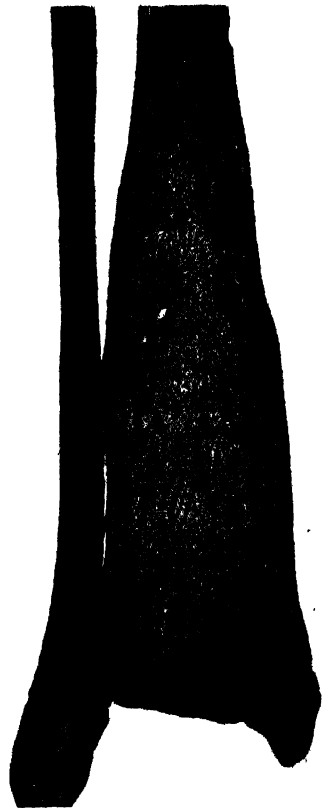


FIG. 92. Tuberculosis of the tibia. The distal part of the diaphysis is greatly thickened by the formation of new bone, of soft, spongy character.

(Museum of Royal College of Surgeons of Edinburgh.)

forms so striking a feature in radiograms. The periosteum is but little affected, and there is little or no new bone formation.

Several gross types of lesion may be recognized, which represent gradations in the progress of the disease or in the reaction of the surrounding tissues.

The Encysted Type is simply a chronic circumscribed tuberculous focus in a healing state. The focus is of small size, and consists of gelatinous material with little caseation. It is walled off by fibrous tissue, which may be so dense as to permit of its total eradication.

The Infiltrating Type results from actively spreading disease and poor reaction, and the whole appearance is that of a progressive tuberculous infiltration. The focus of disease is larger, and the whole process more extensive. At the centre of the affected area there is extensive caseation and around this there is an irregular wide band of grey, translucent, tuberculous granulation tissue, and beyond is a zone of cellular reaction and hyperæmia.

The Atrophic Type is uncommon, and occurs typically in one situation, at the proximal end of the humerus. It is characterized by widespread decalcification and absorption of the bony framework, which is replaced by dry, crumbling, caseous material (*caries sicca*).

The Hypertrophic Type is a rare form in which there is new bone formation and sclerosis instead of the usual decalcification and resorption. This type generally indicates a mixed septic or syphilitic affection. When mixed infection occurs, massive sclerotic portions of the bone may undergo necrosis and form sequestra.

Pathology of Joint Tuberculosis

The relation of joint tuberculosis to bone tuberculosis has already been discussed, and it has been stated that, by the consensus of opinion, the arthritis is usually secondary to a tuberculous focus in the adjoining bone. In a proportion of cases, especially in the knee, the joint is infected directly by blood-borne organisms.

The *synovial membrane* is usually the site of the initial infection, and it



FIG. 98. Tuberculosis of the elbow with superadded septic infection. The articular cartilage has been destroyed, and the exposed bone is decalcified and spongy. Around the joint are numerous out-growths of new bone, a result of the superadded infection.

(Museum of Royal College of Surgeons of Edinburgh.)

always shows greater changes than other parts of the joint. Generally, the earliest tubercles appear near the line of reflection of the synovial membrane to the bone, for this part lies in closest relation to the blood supply and to the original focus in the bone. Tubercles develop in the connective tissue of the synovial membrane, and the usual cellular response that characterizes tuberculosis elsewhere is seen.

The *articular cartilage* suffers disintegration as a secondary process. The disease may affect the cartilage either from its surface or from below, with results that differ greatly in extent and severity. Superficial or perichondral involvement is the commoner form, and fortunately less severe than the subchondral one. Perichondral involvement is due to encroachment of the thickened inflamed synovial membrane, which spreads in the form of a "pannus" over the joint surface. Under this pannus the cartilage becomes softened and disintegrated; the polish of its surface is lost and the cartilage becomes dull, pitted and eroded. Deep or subchondral involvement is the more serious, but fortunately the less common form. Here the disease spreads along the vascular bone deep to the cartilage and separates it from the surface on which it lies. As a result large fragments of cartilage are raised, devitalized, and cast off as loose flakes into the joint.

The bones related to the joint may be involved by spread of the disease, but, even when not actually infected, they show more or less reactive changes. Decalcification of the bone is a well-defined feature, and in the large sponge-like spaces the bone marrow is replaced by cellular and fibrous connective tissues.

The soft tissues around the joint undergo degenerative changes that together give the appearance known as "white swelling." Ligaments and tendons become oedematous, stretched and lax, and muscles undergo atrophic changes. All the tissues are swollen and oedematous and have a pale gelatinous, glistening appearance. Not uncommonly, cold abscesses may track through the soft tissues around the joint, and ultimately form sinuses.

The synovial fluid is increased in amount, usually to a moderate degree, rarely to excess. The fluid is usually watery and somewhat turbid, or it may be purulent.



FIG. 94. Tuberculosis of the elbow with superadded septic infection. (Same case as in Fig. 93. Posterior aspect.)

(Museum of Royal College of Surgeons of Edinburgh.)

Several gross types of joint disease are described. The commonest, in which the disease is of slow progress, and not very virulent, is known as *chronic tuberculous arthritis*. The *fungating* or *granulating form* is rarer, and occurs where the disease is somewhat more severe and rapid. The striking feature is great swelling of the synovial membrane, which protrudes into all parts of the joint as a soft, congested, spongy mass like granulation tissue. The *fibrous form* is a relatively mild, chronic type of the disease. Usually the joint is distended by watery turbid fluid, and when this is present in excess the term *hydrarthrosis* may be applied. Multiple loose bodies, of the "rice grain" fibrinous type, are not uncommon. *Acute tuberculous synovitis* is a rare form, in which the disease runs a rapid acute course, like that of acute suppurative arthritis, for which it is liable to be mistaken.

Tuberculosis of Special Bones and Joints

Tuberculosis of the Vertebrae (Pott's disease). The spine is the commonest site for bone tuberculosis, and one of the most unfavourable,

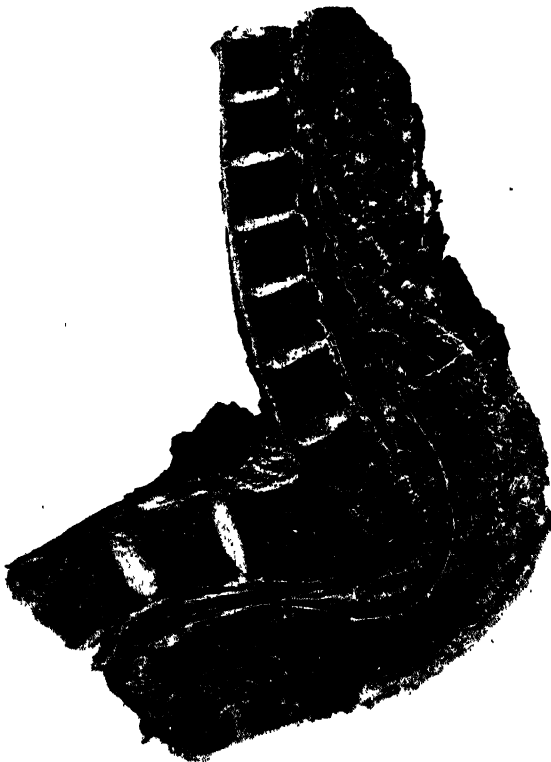


FIG. 95. Tuberculosis of the thoraco-lumbar spine ; with bony union in acute angular kyphosis.

(Museum of Royal College of Surgeons of Edinburgh.)

for the spinal column is subject to so many strains in weight-bearing and is so deeply placed that the earliest manifestations are obscure,

complete immobilization is difficult to obtain, and postural deformities with secondary complications are common. Spinal disease is commonest in children, especially in those under five years, but may occur at any age. In adults the prognosis is usually grave.

The vertebræ of the lower thoracic and the upper lumbar regions, especially the last three thoracic and the first and second lumbar, are most liable to the disease, though no part is exempt. The susceptibility is generally attributed to great range of mobility as well as a considerable amount of weight-bearing in the lower thoracic and upper lumbar regions.

As a rule two adjoining vertebræ are affected, occasionally three or four. Rarely there are two unrelated foci at different levels in the vertebral column.

In children the earliest lesion generally lies in the centre of the body of the vertebra; in adults not infrequently the tuberculous process begins under the periosteum on the anterior surface. Rarely it lies in the vertebral body close to the intervertebral fibro-cartilage, and more rarely still in the spine, laminae or transverse processes. It is said that the usual localization of the disease to the centre of the vertebral body depends upon the anatomical distribution of blood vessels, for this part is supplied by the principal nutrient artery, a small branch of the posterior spinal artery, whereas the upper, low and anterior surfaces have a different blood supply. In adults a greater portion of the blood reaches the surface of the vertebral body, by branches from the cervical, intercostal, or lumbar arteries.

*The progress of the disease may be greatly modified and aggravated by the occurrence of collapse of the body of the affected vertebra. Such collapse is an incident of some importance, for it may lead to complicating factors: (1) mechanical deformity of the spinal column, (2) dissemination of pus and tuberculous products into neighbouring tissues, and (8) involvement of the spinal cord.

(1) The deformity is usually simple kyphosis, but sometimes a certain degree of scoliosis is added. The extent of the deformity varies greatly in different parts of the column; in the cervical spine the roots of the transverse processes lie almost directly lateral to the vertebral bodies, and tend to prevent or minimize deformity; in the lumbar region the column is so broad and deep, and its ligaments and cartilages are so firmly attached, that deformity is rarely more than a diminution of the normal lordosis; but in its thoracic part the column is weak and the pedicles of the vertebræ lie well behind the vertebral bodies, and consequently the deformity is often great. The deformity may be a gradual bend, but often there is an acute angulation or gibbus.

The effects of the kyphosis may be severe. When the angle is in the upper thoracic region the sternum is depressed and the whole thorax flattened; when in the lower thoracic region the thorax is pushed forwards and compressed from above down; and in either case there is interference with expansion of the chest and considerable displacement of the heart and great vessels.

(2) Dissemination of tuberculous products from the collapsing bone leads to the formation of a cold abscess. At first the abscess lies closely adjoining the diseased bone, limited anteriorly by the prevertebral

fascia, and it may spread beyond these confines in various directions according to the anatomical planes in the affected part. In the neck an abscess may pass anteriorly into the pharynx, or laterally to the skin of the posterior triangle, or it may track downwards into the mediastinum. In the thorax an abscess may occupy the mediastinum, or point at the surface or pass behind the diaphragm. In the lumbar region the abscess usually enters the psoas sheath and spreads to the iliac fossa, the pelvis or the groin.

(8) Involvement of the spinal cord (*Pott's paraplegia*) occurs in approximately 10% of cases of spinal tuberculosis, and constitutes a very grave complication. Occasionally the cord is pressed upon by a cold abscess, by a sequestrum, or as a result of pathological dislocation of a vertebra, but in the great majority cord involvement is due to œdema and vascular changes, associated with thickening of the dura mater in contact with tuberculous *débris* displaced backwards from the diseased vertebra. It must be remembered that except in the upper cervical region the cord depends for its blood supply upon small segmental vessels which reach it by passing along the nerve roots from vessels in the extradural space. Consequently, when the extradural tissues are filled with tuberculous material, the corresponding segments of the cord are very liable to venous congestion and œdema. In these cases the dura mater is often thickened and fibrous, and formerly was regarded as the site of tuberculous pachymeningitis; recent observations make it clear, however, that the dura mater is rarely tuberculous, and indeed it generally offers a very resistant barrier to the spread of the disease.

The paralysis is generally of spastic type, for the vascular changes in the cord tend to involve the anterior columns first. At first the gait is unsteady and there is a sensation of walking on wool; later, a spastic paraplegia develops. If special precautions are not taken, contractures may develop at the hip, knee and ankle, owing to the unopposed pull of the more powerful muscle groups. In severe cases there are (1) loss of sphincteric control with the risk of ascending urinary infection, (2) trophic loss with risk of bedsores, (3) sensory paralysis, and (4) flaccid paralysis. These complications influence the prognosis, and the mortality from Pott's paraplegia is over 80%.

Two clinical types are recognized, according to the time of onset of the paralysis in relation to the osseous disease:—

(1) *Early onset*. In this type the symptoms of cord involvement arise during the first year or two of active bone disease. If due to œdema and vascular changes the paralysis comes on gradually and increases in severity as the bone disease progresses. In the majority of cases, after a few months or even as long as a year, when the bone disease reaches a healing phase the paralysis also diminishes, and may even pass off completely.

If, on the other hand, it is due to the pressure of an abscess or a sequestrum, or to a pathological dislocation of the vertebræ, the paralysis comes on more rapidly and is permanent. The same applies to the rare cases in which paralysis results from thrombosis of the segmental blood vessels supplying the cord.

(2) *Late onset.* In this type the symptoms of cord involvement arise years after apparent arrest of the bone disease. They are generally due to mild vascular changes in the cord. The paralysis is usually incomplete and recovery is likely.

Tuberculosis of the Atlas and Epistropheus. This condition presents such distinctive features as merit separate consideration. Here the disease affects the articulations between the occipital bone and the atlas, and between the atlas and epistropheus, as well as the bones themselves. The joint cartilages are extensively destroyed, and parts of the bones, *e.g.*, the odontoid process, may undergo sequestration. There is a special tendency for the atlas to be displaced forwards on the epistropheus. If this occurs suddenly death results immediately from impingement on the cord, but if the movement is very gradual, considerable displacement may do no harm. Caries of the upper cervical vertebræ may give rise to a chronic form of retropharyngeal abscess.

Tuberculosis of the Hip Joint. Like most forms of joint tuberculosis, that at the hip occurs most commonly in childhood. It arises most often between the ages of three and six years, and is progressively less frequent at later ages. In adults, tuberculosis of the hip more often represents recrudescence of an old-standing disease than a fresh infection.

The infection may be primarily osseous or synovial. It is generally stated that the initial focus is osseous in 75% of cases, but modern radiological investigation of early cases does not bear this out, and suggests that the infection is more often synovial in origin.

There are two common sites for an initial osseous focus. The first is at the femoral metaphysis near the inferior aspect of the neck of the femur (the so-called Babcock's triangle). At this point the disease is intra-articular, and the infection may spread directly from the bone to the synovial membrane, or it may perforate the epiphyseal cartilage, invade the head of the femur, and erupt at the articular surface. In rare

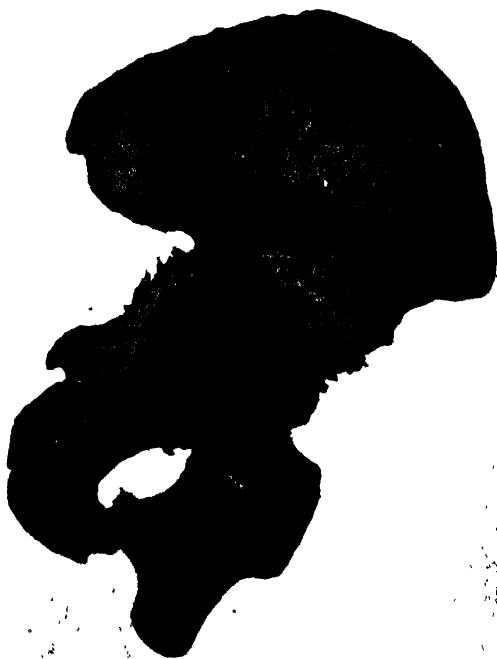


FIG. 96. Tuberculosis of the hip joint. The articular cartilages have been destroyed and the bones eroded, and the femur has assumed a pronounced adduction deformity. The presence of much new bone, which forms numerous marginal osteophytes, indicates that a super-added septic infection had occurred.

(Museum of Royal College of Surgeons of Edinburgh.)

cases, if early treatment be instituted, the disease may remain confined to the bone, and form an encysted focus in the neck of the femur.

The second site for an initial bone focus is in the innominate bone close to the triradiate cartilage. From thence the disease spreads directly into the joint in the region of the pad of fat. It may spread also through the pelvic bone and lead to abscess formation within the pelvis.

In many cases, probably the majority, there is no initial bone focus, and the infection is primarily synovial. Radiological examination at an early stage shows some increase in density of the peri-articular soft tissues, but no other abnormality. Later, diffuse decalcification of both the femur and the acetabulum is a marked feature, and the joint outline becomes indistinct or quite unrecognizable. There is little fluid distension of the joint, but cold abscesses in the peri-articular soft tissues occur in nearly 50% of cases.

The articular cartilages are eroded, and the adjacent bone may be infected. The upper part of the head of the femur and the upper posterior part of the acetabulum undergo greatest destruction at this stage, for these parts are subject to the greatest pressure, particularly if, as often happens, the joint be flexed and adducted. The head of the femur may become greatly deformed, whilst the acetabulum is deepened and enlarged upwards and backwards, the so-called "wandering acetabulum."

The process of healing in tuberculosis of the hip joint is necessarily slow. In cases in which the diagnosis has been established beyond doubt, complete healing with restitution of full movement is extremely rare. In the majority of cases, the disease persists in a quiescent state during many years, and is liable to recrudescence. Movement at the joint remains greatly impaired, owing to deformity of the articular surfaces and fibrosis of the peri-articular soft tissues. Following upon destruction of the articular cartilages, bony ankylosis usually results.

Tuberculosis of the Sacro-iliac Joint. Sacro-iliac tuberculosis is relatively uncommon. It differs from other forms of bone and joint tuberculosis in occurring mainly in adults, generally between the ages of twenty and thirty years. It is rare in children. It may be the only apparent focus of tuberculosis, but more often active disease in the lungs coexists, and the health is gravely impaired.

Sacro-iliac tuberculosis is almost invariably osseous in origin. It generally starts in the sacrum and spreads thence to the sacro-iliac joint and to the ilium. Not infrequently, the lumbosacral articulation is also involved in the extensive destruction of bones.

Development of cold abscesses is an important feature of the disease and, indeed, may provide the first sign of its presence. An abscess forms usually immediately to one side of the joint posteriorly, less often in the iliac fossa and inguinal or femoral region. There may be extension through the gluteal foramina, but extension to the ischio-rectal fossa is exceedingly rare.

Tuberculosis of the Knee Joint. The knee is one of the commonest sites of tuberculous arthritis. It is most often affected in childhood and

early adult life, but the disease is by no means rare in old age, when it may assume a very acute form. The infection is blood-borne, and in the majority of cases arises in a concealed glandular focus, much less often from an active pulmonary lesion.

Pathologically, there are two fairly distinct types of arthritis: (1) synovial, and (2) osteo-arthritic.

(1) The *synovial* is commonest in childhood. The synovial membrane is thick and gelatinous and coated with opaque nodules or tubercles. Microscopically, the lining epithelium is greatly thickened and the supporting fibrous tissue is œdematous and increased in amount and

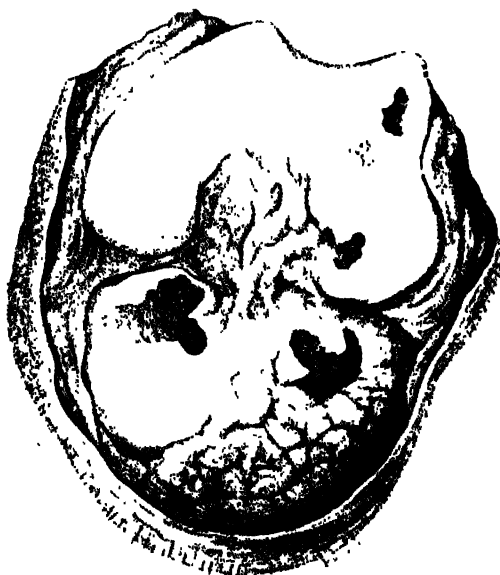


FIG. 97. Tuberculosis of the knee. The articular cartilages over both tibial condyles and the medial femoral condyle have been eroded and destroyed. A large pannus of diseased synovial membrane covers the medial condyle of the tibia.

(By courtesy of Prof. J. W. S. Blacklock.)

may show degenerative changes and caseation. A characteristic feature is hypertrophy of the peri-synovial fat, especially around the suprapatellar pouch and the back of the joint. In many cases fringes—papillary or nodular—project from the synovial membrane and may fill the entire joint space. In almost all instances there is a considerable effusion of clear or straw-coloured fluid, which may be loculated.

The synovial type of disease usually pursues a very chronic course, and, under favourable conditions, shows a pronounced tendency to resolution, often without more than slight loss of movement of the joint. In severe cases caseation with cold abscess formation may occur.

(2) The *osteo-arthritic* variety is characterized by destructive changes in the cartilage and the subjacent bone. In most cases the joint infection is secondary to eruption of caseating foci in the epiphyses. Such foci

are more common in the femoral than in the humeral condyles; they are rare in the patella, but may be confined to it. Occasionally at the lower end of the femur the disease is of a very marked type, involving the diaphysis as well as the epiphysis. The disease may reach the joint at the reflection of the synovial membrane or at any part of the articular surface. Subchondral infiltration of the bones may lead to extensive necrosis of the cartilage, which may become loose and detached. The synovial membrane usually shares in the disease and may become extensively adherent to the ulcerated cartilage. Subluxation of the joint is a common occurrence.

In the osteo-arthritic type of tuberculosis the joint may be greatly disorganized. Healing is usually very protracted and, even in favourable cases, fibrous or osseous ankylosis is the usual result. It is in this variety, especially in adults, that operative measures may be needed to shorten the course of the disease and to secure ankylosis.

Tuberculosis of the Ankle Joint. Involvement of this joint is usually the result of disease in the talus, or of the lower end of the tibia or fibula. The disease is characterized by thickening of the synovial membrane and often by the formation of cold abscesses, which tend to point on the lateral aspect behind the lateral malleolus.

Tuberculosis of the Shoulder. At the shoulder the disease usually begins in the head of the humerus, and the disease is commonest in adult life, not infrequently in association with pulmonary tuberculosis. In many cases the arthritis is of a very chronic type and associated with organization and fibrosis of the tuberculous exudate (*caries sicca*). The cartilage of the head of the humerus is usually destroyed, and the glenoid fossa may be involved in disease or altered in contour by pressure.

Tuberculosis of the Wrist. At the wrist one of the carpal bones is usually affected first, especially the *os capitatum*. From here the infection travels readily to the synovial membrane and to the other bones of the wrist. In young subjects the disease may lead to gross disorganization of the carpus and wrist joint; but in adults it is often more chronic and may culminate in fibro-osseous ankylosis.

Tuberculous Dactylitis (*spina ventosa*). This condition, nowadays uncommon, occurs mostly in children before the age of ten years. Either phalanges, metacarpals or metatarsals are affected and sometimes the disease is multiple and bilateral. In the foot the first metatarsal is most frequently affected. The earliest focus lies near the mid point of the diaphysis—a localization attributable to the disposition of the nutrient artery, which breaks up into fine branches immediately it enters the bone. As the tuberculous degeneration progresses the periosteum of the diaphysis is raised and a shell of new bone develops; its fusiform outline is determined by the relatively firm attachment of the ligaments at the extremity of the bone. When abscess formation and superadded infection occur the pathological appearances of the bone resemble those of acute or chronic osteomyelitis. Growth in the long axis is usually interrupted or inhibited, and the affected bone becomes short and barrel shaped.

Tuberculosis of the Skull and Face. The flat bones of the skull may be attacked by tuberculosis in childhood and in adolescence. The disease is extremely rare. The temporal and frontal bones are those most often involved, and the parietal and occipital bones only rarely. The disease begins as a localized focus in the diploë, in which it may spread to a considerable distance without much evidence on the exterior. At the site of disease the bone is rarefied, until finally the outer table is perforated, and small light sequestra may result. On the inner table the dura mater is thickened by the formation of œdematous granulations, which extend for a considerable distance beyond the osseous lesion.

The facial bones are occasionally affected by tuberculosis. The bone attacked most often is the *zygoma* in its maxillary process; the disease usually terminates in the formation of an abscess, which by rupture results in a sinus situated near the lower margin of the orbit. The mandible is especially liable to attack at the time of the second dentition. Either the ramus or the body may be involved.

Tuberculosis of the Ribs. The ribs are liable to infection in adults more often than in children. Disease at this site is common in association with other tuberculous osseous or arthritic lesions. The disease usually begins in the neighbourhood of the costo-chondral junctions, which correspond to the metaphyses in long bones. The rib is thickened, and an ovoid, elastic swelling may develop in the soft tissues. Abscesses arising from a tuberculous focus in the rib may track for a considerable distance before reaching the surface.

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CHAPTER IX

DISEASES OF JOINTS

HEALTHY joints perform their functions so unobtrusively that their mechanical perfection is often not realized, yet upon their smooth action the efficiency of the whole system of locomotion depends. Stiffness or pain even in a single joint may profoundly hinder the movements of the whole body.

From their delicacy of structure and precision of movement, and from the constant stresses to which they are subject, joints are readily disabled as a result of disease. A joint may be incapacitated by influences which affect its interior (intra-articular lesions) or from changes affecting the structures around it (peri-articular lesions).

Acute diseases of joints are rare, a fortunate circumstance, for their effects are often grave, but chronic diseases are extremely common. Indeed, a deforming arthritis is one of the most usual causes of chronic disability in adults, and joint tuberculosis is frequent in children.

The proper working of a joint depends upon many factors, among which are the free and properly co-ordinated movement of its muscles, the alignment of its bones and the integrity of its ligaments, but most of all upon the condition of its bearing surface, the articular cartilage, and upon its lubrication.

The cartilage, which is of hyaline type, is about 3 mm. thick. It is smooth, hard and highly polished, and it provides an ideal bearing or gliding surface.

The nutrition of articular cartilage is a problem of some interest, for the cartilage itself is entirely avascular, yet nourishment must be essential for its proper vitality. Almost a hundred years ago Toynece showed that in the bone deep to the cartilage there is a rich plexus of blood vessels, and it seems likely that this forms the chief source of nourishment, which no doubt reaches the cartilage by a process of imbibition. Since the blood supply is most copious near the margins of the cartilage this part when irritated frequently proliferates, *e.g.*, in osteo-arthritis; whereas the central part of the cartilage is less adequately nourished and is more liable to degeneration. If a small fragment of cartilage is set free in a joint it may live and actually grow, and it must therefore be assumed that the cartilage can absorb nourishment from the synovial fluid, but since in health the synovial fluid has a very low protein content its nutritive value must be small.

Repair in cartilage is a very slow process, for cartilage cells have little proliferative power. A wound of the cartilage is always repaired by fibrous tissue, and for this reason any damage to the cartilage, whether from injury or disease, may lead to serious interference with joint function and often to fibrous ankylosis.

ACUTE PYOGENIC ARTHRITIS

Infection may reach a joint either (1) directly from an open wound, a compound dislocation, a local abscess or an osteomyelitis, or (2) by the blood stream from some distant focus. The latter variety will be considered in more detail here.

The organisms responsible for this variety of arthritis are usually streptococci, staphylococci or pneumococci. In most cases the arthritis occurs as a complication of a frank septicæmia; occasionally the joint lesion provides the sole evidence that organisms have been circulating in the blood stream. Not infrequently infection is derived from the throat, or from suppurative processes elsewhere in the body, such as a whitlow or puerperal endometritis. The hip joint is most often affected. The severity of the arthritis varies greatly and is determined by the virulence of the organisms. Staphylococci generally lead to such gross pathological changes in the joint as effectively prevent functional recovery, whereas streptococci may cause either a fulminating or a relatively mild, subacute attack.

The synovial membrane becomes greatly swollen and congested, and from œdema assumes a soft, almost jelly-like consistency. Coincidentally the joint becomes distended with fluid, at first of watery consistency but containing pus cells and fibrinous flakes, later purulent.

The cartilage loses the glisten of health and becomes undermined, so that portions of it may become detached, leaving the bone exposed and bare. The soft parts are infiltrated with inflammatory products and become softened and stretched. Escape of the purulent effusion leads to abscesses, which develop in the soft tissues and burrow in various directions. The bone abutting on the joint may undergo absorption and permit subluxation or dislocation of the joint.

Acute pyogenic arthritis may cause much pain and great constitutional reaction. In the course of septicæmia or pyæmia, however, the symptoms may be masked by those of the general infection. In these circumstances damage to the joint is not necessarily great, and aspiration of the pus may suffice to restore the function of the joint.

PNEUMOCOCCAL ARTHRITIS

This may occur in the course of pneumococcal septicæmia, or as a complication of pneumococcal disease in the lungs or elsewhere, or, rarely, as a solitary affection. It is most common in children. Unlike pneumococcal peritonitis of children, it is equally common in the two sexes. The course of the disease is very variable. Usually it is mild in type, the fluid remains thin and watery for a long time, and the cartilage is little affected; but occasionally the arthritis is associated with severe toxæmia. When it arises in the course of general septicæmia the joint disease may pass unnoticed.

In adults, pneumococcal arthritis usually follows pneumonia. It is especially apt to begin about a week or ten days after the onset of the infection, either at the time when the crisis is expected or shortly after it. The joint affected is usually a large one, such as the knee or hip.

Rarely several joints may suffer simultaneously. The articular lesion varies from a relatively mild synovitis to a severe infection of all parts of the joint. The fluid is at first watery, but usually suppuration ensues, and the joint fills with thick odourless pus, often slightly greenish in colour and sometimes containing thick fibrinous coagula. The pus usually contains pneumococci, but it may be sterile.

TYPHOID ARTHRITIS

A joint may be affected in typhoid fever at any time during the acute stage of the disease or when it is subsiding. The hip is the joint most often involved, and the infecting organism may be *B. typhosus*, alone or mixed with *B. coli* or others. The arthritis may run a mild or severe course, with or without suppuration. Destruction of bone is a not uncommon result and may lead to dislocation.

Scarlet fever, *measles* and other zymotic diseases may also be complicated by arthritis, which is usually of mild type and non-suppurative. In *acute rheumatism* arthritis is, of course, often one of the most obvious features. These diseases are seldom of surgical significance.

GONOCOCCAL ARTHRITIS

It is said that infection of joints occurs in from 2% to 5% of cases of gonorrhœa. Men are affected most often, but women and even infants are not exempt. The primary focus of the disease in the great majority of cases lies in the urethra, prostate or seminal vesicles; but arthritis may occasionally complicate vulvo-vaginitis or gonorrhœal ophthalmia.

Involvement of the joints results from actual infection by gonococci, borne in the blood stream, but it is rarely possible to demonstrate the organisms in fluid withdrawn from the joint, and for diagnosis reliance must be placed on such circumstantial evidence as recognition of the primary focus, demonstration of changes in the blood by complement-fixation tests, and the effect of treatment.

Often only one joint, and that commonly the knee, is affected, but sometimes there are several, especially the knee, elbow, wrist, ankle, the joints of the fingers and the temporo-mandibular joint; occasionally the joints of the vertebral column are involved. The joint infection usually appears about three weeks after the onset of the primary lesion, but it may arise at a much later stage, when there remains only a hidden focus in the prostate, and the only sign that persists is merely slight "gleet." The intensity of the arthritis bears no relation to the extent and severity of the original infection, but in general the earlier its onset after the urethritis the more intense its effects. Apart from the arthritis there may be other evidence of hæmatogenous infection. Other serous surfaces may be involved, such as tendon sheaths and bursæ. Rarely endocarditis, pleurisy or meningitis may occur, and fasciæ and aponeuroses also may suffer.

The intensity of the joint disease varies greatly, and there may be a transient affection that is hardly recognizable or a severe lesion that

causes much suffering, and great and permanent deformity. There is a definite tendency for the arthritis to recur with every exacerbation or fresh attack of gonorrhoea.

The following principal types are recognized.

(1) **Acute Gonococcal Arthritis.** In this type the virulence of the infection is great and its effects are correspondingly severe. A large joint such as the knee or elbow is commonly involved. The onset of the synovitis is rapid, with pain and constitutional symptoms. The joint becomes distended with turbid fluid, and there is considerable inflammatory change in the periarticular tissues. The skin assumes a fiery red colour and the local temperature is raised. The disease may subside after a short acute phase, but often resolution is imperfect and the joint movements remain limited by fibrous periarticular adhesions.

Occasionally the joint fills with pus, there are acute inflammatory changes in the synovial membrane, the cartilages undergo destruction, and abscesses may form in the soft tissues. This suppurative type is generally due to secondary infection with pyogenic organisms.

(2) **Chronic Gonococcal Arthritis.** This is much more common than the acute affection. It occurs in two forms—the dry form and the hydropic form. The *dry form* of chronic gonococcal arthritis is usually polyarticular in distribution. The infection is of low virulence, and the disease is not acute, but it is apt to persist for a long time and to cause great disability. Most often the wrists and the small joints of the hands are affected, or the disease may attack one or more larger joints. The onset is insidious, with pain and stiffness of the joint and redness of the skin. The synovial membrane and periarticular soft tissues are infiltrated with inflammatory cells and are oedematous, but there is little or no increase of fluid in the joint. The disease may subside completely, but very commonly fibrosis occurs, both in the joint and in the soft parts, and as a result stiffness persists or increases. Actual fibrous ankylosis may occur, often with severe contraction deformities. This type of disease bears a close resemblance to the polyarticular form of chronic rheumatoid arthritis, for which it may be mistaken.

The *hydropic form* of chronic gonococcal arthritis may involve one or more of the joints, usually large joints, such as the knees, which gradually become distended with serous or sero-fibrinous fluid. There is little or no inflammatory reaction around the joint and there are no constitutional symptoms. Movements of the joint are relatively painless and comparatively unrestricted, except by the mere presence of articular effusion. Usually the disturbance subsides but relapses are apt to occur.

SYPHILITIC ARTHRITIS

Syphilis, unlike tuberculosis, rarely gives rise to serious affections of the joints, and syphilitic arthritis is generally regarded as a very uncommon condition. Those who have made a special study of the disease, however, claim that it is not really so infrequent, and it is possible that many cases go unrecognized, or pass as examples of rheumatoid arthritis.

In acquired syphilis the joints may be affected at any period after the spirochætes have reached the blood stream, and at any stage the lesions may be mild or severe.

In the secondary stage the lesions are usually of mild character. Transient pains in the joints (arthralgia) are not uncommon at the time of the skin rashes, and it is possible that these indicate a fleeting affection of the synovial membrane.

Sometimes in the secondary stage there is a painless distension of the joint by clear watery fluid (syphilitic hydrarthrosis). It is usually transient, but occasionally may persist for long periods. The knee joint is especially liable to be affected, and the lesion is often bilateral.

In the late secondary or early tertiary stages a plastic form of syphilitic arthritis may occur. Usually it is monarticular, and the knee, elbow or mid-tarsal joint is particularly liable to be involved. Sometimes, however, it is polyarticular, and may attack the carpus and the small joints of the fingers. In its pathological features it sometimes resembles arthritis deformans, for which it may be mistaken.

The joint is swollen by œdema of the soft tissues rather than by an intra-articular accumulation of fluid. What fluid is present is turbid and thick, containing great numbers of lymphocytes, and the fluid gives a strongly positive Wassermann reaction. The synovial membrane is greatly thickened and infiltrated with lymphocytes, and the extra-articular soft tissues may show a "white swelling" not dissimilar to that of tuberculosis. With antisypilitic treatment complete resolution is to be expected, but if untreated the disease may progress to fibrosis and much deformity, and secondary degeneration of the cartilage may lead to partial ankylosis.

In tertiary syphilis and in inherited syphilis there may occur a gummatous arthritis. Two forms of this are described (Axhausen), the synovial and the osseous forms, according to the primary site of the lesion. In either case there is great thickening of the synovial membrane and an excess of fluid collects in the joint. The cartilage may be eroded and irregular, and there may be a gummatous osteitis in the adjacent bones.

In inherited syphilis the same types of joint lesion may occur, and may be bilateral. They occur most often in the knees, and commonly arise at the time of or just before puberty. In addition, the joints may be involved by spread of the disease from the neighbouring epiphyses (*see Syphilitic Osteochondritis*, p. 128).

ARTHRITIS DEFORMANS

It seems likely that this is a medley of diseases rather than an entity, and it may be said to include all those chronic affections of joints for which no specific cause is at present known. Only comparatively recently have the articular lesions of rheumatism, gout and gonorrhœa been differentiated, and probably in the future other equally specific diseases will be distinguished.

The subject is confused by a baffling terminology, the result of different views in regard to the ætiology. Some of the names are

variously applied to the whole disease or to any of its separate parts, and none is universally acceptable. The nomenclature employed here is the one at present in most general use; "arthritis deformans" is used as a generic term only.

At present the evidence clearly warrants the recognition of two principal sub-groups, typically quite distinct but linked by intermediate or "mixed" forms:—

- (1) **Rheumatoid arthritis** (synovial or proliferative type; chronic infective arthritis).
- (2) **Osteo-arthritis** (chondro-osseous or degenerative type).
- (3) **Intermediate or mixed forms.**

RHEUMATOID ARTHRITIS

This disease bears no recognizable relationship to rheumatic fever or other rheumatic affections, and the title "rheumatoid" is only justified by common usage. Rheumatoid arthritis is a polyarticular affection, often bilateral and symmetrical, most commonly involving the metacarpo-phalangeal and proximal interphalangeal joints of the hands and the smaller joints generally. The wrist, ankle, shoulder and the temporo-mandibular joints are also subject to the disease, though to a less extent. The disease affects women three or four times more often than men. It occurs at any age, but usually in adults of less than forty years.

The Pathological Process. The onset of the disease may be marked by an acute or subacute phase, or the progress may be insidious throughout. The joints become swollen and tender, fixed by muscular spasm and painful on the slightest movement, and this state may continue for weeks or months. Later fibrosis sets in, with mechanical restriction of the joint movements and often with much crippling from contraction deformities.

The course of the disease is that of a subacute or chronic inflammation, the main effects of which fall upon the synovial membrane and other soft tissues. The cartilage and bone are also affected, but usually as a secondary process. The synovial membrane is invaded by lymphocytes and plasma cells, and becomes congested and œdematous. It is greatly swollen, and projects into the joint as red, proliferating, spongy masses, which fill up every available space in the recesses of the joint and creep as a web or pannus over the surface of the articular cartilage, often eroding it. When, in the later stages, the inflammatory process subsides there is much proliferation of fibrous tissue, which fixes bare portions of the bony surfaces and leads to severe contraction deformities.

As in many situations where inflammation has subsided, there is a great tendency to the accumulation of adipose tissue in the synovial fringes; such a condition, if extensive, is known as *lipoma arborescens*. Occasionally also small islands of cartilage or even of bone may appear in the fringes, though this is more characteristic of osteo-arthritis.

The synovial fluid is usually reduced below the normal quantity. The cartilage becomes atrophied and thin, as may be recognized in

radiograms by diminution of the interval between the bone shadows. The bone becomes rarefied, partly on account of the inflammatory process and partly from disuse. When a severe contraction deformity exists, part of the bone may become absorbed, and allow of subluxation. Intra-articular ligaments suffer when the bone is affected, and become eroded and disintegrated. The long head of the biceps, for instance, as it passes through the shoulder joint may disappear completely. The articular capsule and extra-articular soft tissue are much affected, being at first swollen and cedematous, and giving the enlarged joint a fusiform shape. In the later stages fibrosis in these tissues, together with similar changes in the joint, leads to the fixation and deformity which form such a disabling feature of the disease. The skin over the joint becomes thin and bluish-white, its surface dry and shiny.

Ætiology. Many theories have been advanced in regard to the ætiology of rheumatoid arthritis and still it remains unsolved. Briefly, the main groups of theories may be classified as the non-infective and the infective. In the former group are such factors as congenital predisposition and endocrine disturbances, of which it is impossible to say more than that they remain unproved. It has been suggested that an important part is played by disorders of metabolism, and delay in the removal of ingested glucose from the blood, faulty elimination of sulphur, and abnormal phosphorus metabolism have all been suggested; This very multiplicity, however, precludes conviction.

There can be no doubt that in a large proportion of cases the disease is closely related to some infective or toxic condition. Not infrequently there is a history that the onset of the joint disease has been preceded by an exacerbation of some infective focus in the upper air passages, in the abdomen, or elsewhere, and a temporary "flare-up" of the joint disease with subsequent improvement is a common result when such a focus is removed. Moreover, in adults occasionally, and in children more often, there are other signs of chronic infection, such as sallow complexion, enlargement of lymph glands, and occasional pyrexia. In children also the spleen may be enlarged (Still's disease). It is interesting to note that often there is an absence of hydrochloric acid from the gastric contents and that the bacterial flora of the stomach and upper intestine is greatly altered and increased. It is possible that toxic absorption from this source plays an important part in the ætiology.

Bacteriological examination of the joints is usually negative; a few workers have claimed to be able to isolate streptococci, diplococci or other organisms with regularity, but confirmation of such findings is lacking. More probably the joints are affected by toxins derived from distant septic foci. It has been suggested that the affection is an allergic one, and that from repeated exposure to allergic influence the joints are rendered hypersensitive to small doses of toxin.

OSTEO-ARTHRITIS

This is an age-old affliction of mankind. Ruffer has described many interesting specimens obtained from the tombs of ancient Egypt,

including examples of spondylitis and of osteo-arthritis of the hip, shoulder and other joints. Osteo-arthritis has even been found in skeletons 6,000 years old. Lower animals are also subject to the disease, both in captivity and in their natural haunts.

In typical instances osteo-arthritis differs greatly from rheumatoid arthritis. It affects adults and old people, especially males; it mainly affects one joint at first (though others may be involved to a less degree), and it affects articular cartilage and bone principally, synovial membrane to a less obvious extent. This general statement, however, is subject to qualification, for intermediate forms are common.

Osteo-arthritis affects the knee most often, then the hip (*malum coxæ senilis*), the metacarpo-phalangeal joint of the thumb, and the corresponding joint of the great toe. In elderly people a mild, though sometimes disabling, form of osteo-arthritis is often seen in the joints of the fingers. The joints, ligaments and cartilages of the vertebral column may be affected, and constitute the condition known as spondylitis deformans, which will be described separately (*see p. 301*).

Morbid Anatomy. The pathological process affects cartilage and bone primarily and principally, the synovial membrane and other soft tissues only at a later stage. Cartilage and bone undergo changes which are both degenerative in nature but also to a great extent proliferative.

Fisher has emphasized the fundamental differences between the changes near the centre of the joint surfaces and near the periphery. The central part of the articular cartilage is comparatively ill-nourished, and, moreover, bears the brunt of the body-weight or other forces, whereas the peripheral portion is adequately nourished and little subject to pressure. Consequently the changes in the central area are principally degenerative; those at the periphery chiefly proliferative.

The central part of the cartilage is affected first. It undergoes degenerative changes whereby it becomes dull and velvety and of soft consistency. Microscopically, the earliest change is in the smooth hyaline matrix of the cartilage, which becomes fibrillated and frayed. The cartilage cells lose their regular arrangement, and they become swollen and eventually disappear. Sometimes whilst the greater portion of the cartilage is worn away small areas remain unaffected and form smooth rounded eminences on the articular surfaces—*epi-articular ecchondroses*.

At the periphery of the joint surface the cartilage proliferates and forms large irregular masses—*peri-articular ecchondroses* or *chondrophytes*—which may fringe the entire joint like an extension of its articular surface, or may flank it like irregular buttresses, or again may project in polypoid fashion. Such outgrowths usually become ossified and may then be called *chondro-osteophytes*. Sometimes they form a complete collar round the joint and interfere greatly with movement.

When the cartilage is worn away, the bone at the joint surface becomes exposed, and often undergoes a curious change known as *eburnation*, whereby parts of its surface become dense, smooth and shiny like porcelain or ivory. In hinge joints such as the elbow or knee the to-and-fro gliding movement may give rise to an alternation

of cartilage-covered ridges and grooves. The bone is decalcified, porous and light, and near the joint it is sometimes replaced by areas of fibrous tissue in which small cysts may develop. Softening of the bone may lead to secondary deformities, as at the hip, where coxa vara may occur with shortening and apparent broadening of the neck and sometimes extensive resorption of the head.



FIG. 98. Osteo-arthritis of the knee. A specimen obtained post-mortem from an elderly person who had not complained of symptoms referred to the joint. Numerous fibro-fatty villous masses project from the synovial membrane. Note that the suprapatellar bursa is unaffected.

(Museum of Royal College of Surgeons of Edinburgh.)

The synovial membrane is affected at a relatively late stage. It is thickened, and from its surface there project into the joint numerous processes, which may be fine, delicate and filamentous, or coarse and pedunculated (*synovial villi*). These are very liable to be nipped between the joint surfaces, when temporary increase of fluid in the joint results, with exacerbation of pain and disability. Masses of cartilage may grow in the synovial fringes (*synovial chondromata*) from small islands of cartilage cells normally present. They may attain large size and may become calcified or even in part ossified. In other cases masses of fat accumulate in the synovial fringes and project into the joint (*lipoma arborescens*).

Loose bodies are of very frequent occurrence in osteo-arthritis. The majority of the loose bodies arise from detached synovial fringes, and hence may be composed entirely of fibrous tissue or may contain fat or cartilage. Usually in the last variety some calcification is present, and often true bone. Other bodies arise from the detachment of portions of periarticular or epiauticular chondrophytes (see p. 209).

Heberden's nodes are small rounded bony outgrowths which arise from the bones of the fingers and project under the skin. They are common in osteoarthritis and are usually multiple and symmetrical. They lie close to one of the interphalangeal joints, commonly the

terminal ones. Often they lead to deviation of the terminal part of the finger and to flexion or extension deformity. Usually they cause little disability but occasionally they give rise to limitation of movement.

Pathogenesis of Osteo-Arthritis. The most noteworthy feature in the pathology of osteo-arthritis lies in the close association of degenerative and proliferative changes—the articular cartilage over the centre of the joint surface is softened and worn away, whereas that at the periphery is stimulated to grow. It seems most satisfactory to attribute this differential effect to the fact that the central part of the cartilage is poorly nourished and moreover is subject to the constant pressure of the opposed articular surface, whereas the peripheral parts of the cartilage are better nourished and are subject only to intermittent pressure.

In a large proportion of cases there is evidence that trauma plays an important part in the development of the arthritis. Thus a mobile medial meniscus or a loose body may in the course of time lead to arthritis; in other cases there are occupational strains, or stresses from faulty statics, as at the knee joint after malunited fracture, or in knock-knee, or at the first joint of the great toe in flat-foot. It cannot be accepted, however, that trauma alone can cause osteo-arthritis; it merely determines the involvement of certain joints in persons who for other reasons are susceptible to the disease.

It seems possible that in some cases the predisposing factor is a chronic low-grade toxæmia derived from distant septic foci, such as are frequently present. Llewellyn and others have upheld the view that the general predisposing factor is some derangement of metabolism or of the internal secretions, for osteo-arthritis commonly occurs at the climacteric and may be associated with hypothyroidism or other endocrine affections.

According to Fisher, the fundamental feature of the disease lies in disturbance of the nutrition of the articular cartilage. In some cases the malnutrition results from long-continued absorption from septic foci; in other cases, from the effects of trauma; or possibly, in old subjects, from sclerotic changes in the arteries. It is possible that changes in the nutritive quality of the synovial fluid are responsible.

NEUROPATHIC DISEASE OF JOINTS (Charcot's Joints)

In 1868 Charcot described a peculiar joint affection that follows diseases of the central nervous system. In 80% of cases this neuropathic



FIG. 99. Osteo-arthritis of the shoulder. Note the eburnation of the head of the humerus and the osteophytes at the margin of the articular surface.

(Department of Surgery, University of Edinburgh.)

"arthritis" is due to *tabes dorsalis*; in most of the remainder it is due to *syringomyelia*, but it may rarely follow cerebral diplegia, myelitis, and other lesions of the brain, cord, and peripheral nerves. In *tabes*, since the nerve lesion affects the lower part of the spinal cord, the joints affected are almost always those of the lower extremity. Most often the knee is involved, less frequently the hip or the ankle. Occasionally two joints are involved, either simultaneously or in succession. In *syringomyelia*, since the cervical part of the spinal cord is affected, the joints of the upper extremity are most liable to involvement. The arthropathy of *syringomyelia* almost invariably affects the shoulder.



FIG. 100. Tabetic arthropathy of the knee. The lateral condyle of the femur and the head of the tibia have been eroded. From the proximal end of the tibia a large shelf of new bone projects forwards.

Department of Surgery, University of Edinburgh.)

"Charcot's disease" is a term now generally restricted to the joint manifestation of *tabes*, but this differs from that of *syringomyelia* in no fundamental feature except in causation. "Charcot's disease" is a para-syphilitic or meta-syphilitic affection, which is not due to any direct effect upon the joint by the spirochaetes or their toxins, but is secondary to a loss of trophic influence or some other change resulting from the nerve lesion. It has been estimated that "Charcot's joints" occur in about 3% of patients suffering from *tabes*. The joint lesion may arise at any period of the disease, even at an early stage, so rendering its recognition difficult.

Appearance of the Affected Joint. The pathological changes are remarkable in that there is at the same time extremely gross destruction of bone and articular cartilage, and often equally gross irregular new formation around the joint. The whole process develops with rapidity and with an entire absence of pain.

The first morbid change appears to consist in decalcification and resorption of the articular ends of the bones, and occasionally this can be recognized in radiograms before there is any visible affection of the joint itself. As a result of some degenerative process the articular ends of the bone become soft and friable, and in this state, favoured by the absence of pain, the bone crumbles as a result of weight-bearing and friction. The articular end of the bone is rapidly eroded, often with the formation of irregular grooves and ridges, and eventually large portions of it may disappear. Often the joint contains massive loose bodies. At the hip, the head and neck of the femur may vanish entirely, as though by the action of some corrosive agent (see Fig. 101).

At the knee the ends of the tibia or femur may be destroyed, or one condyle may disappear while its fellow remains relatively unaffected.

Coincident with the degenerative changes there is irregular production of cartilage and bone, so that chondrophytes and osteophytes appear at the margins of the joints and in the substance of the capsule, forming irregular friable masses, which may be detached as loose bodies.



FIG. 101. Tabetic arthropathy of the hip (Charcot's joint). Note the gross destruction of bone and its extensive regeneration. The original acetabulum has disappeared completely, and a greatly enlarged joint cavity is surrounded by an irregular rim of new bone. There are several large masses of loose bone, which occupied the synovial membrane and the peri-articular tissues.

(Museum of Royal College of Surgeons of Edinburgh.)

The synovial membrane shares in the destructive changes and becomes softened, disorganized, and infiltrated with granulation tissue. The capsule, intra-articular ligaments, and tendons may disintegrate and disappear, the peri-articular soft tissues are swollen with œdema far beyond the joint, and the overlying skin may be erythematous and congested.

As a result of the bone deformities and of the laxity of the articular capsule the joint often becomes dislocated. The soft parts stretch greatly and the joint forms a thick voluminous bag, and may even open into bursæ or the neighbouring joints. Thus at the ankle the joint

may ultimately include the whole of the talus and other tarsal bones. The interior of the cavity is lined by a rough granulating membrane from which project polypoidal chondro-osseous masses. The fluid of the joint is viscid, yellow, or often blood stained.

Types of the Disease. Three pathological types have been described, according to the relative extent of the destructive and regenerative changes. The commonest form of the disease, seen most often in the knee in tabes, and characterized by much new bone formation, has been termed the *hypertrophic type*. The form seen in the shoulder, or less often in the hip, in which new formation is not evident and destruction predominates, has been called *atrophic*: and the rare form in which both destruction and new formation occur in but limited degree, and in which the changes resemble those of arthritis deformans, is known as "*osteo-arthritis*." It is evident that these so-called "types" are merely variations from the average, and the classification has a clinical rather than a pathological value. It seems probable that the extent and character of the changes depend to some degree upon the amount of movement that the joint has been allowed.

The Cause of the Disease. The cause of neuropathic joint disease, the relationship of destructive changes on the one hand and of new formation on the other, and the dependence of the whole process upon some perverted nerve influence, form a study of particular interest from the standpoint of the physiology of bone formation.

It is abundantly clear that the fundamental process is one of degeneration or destruction. New bone formation is a later process, and probably is attributable to the liberation of a vast amount of calcium, which readily precipitates in any ossifiable medium in the vicinity.

It is not clear how disease of the central nervous system produces these effects, for removal of trophic influences alone is insufficient to account for them. It seems probable that the repeated trauma permitted by the absence of pain is an important factor, for Eloesser has shown experimentally that after section of the posterior nerve roots to a limb, joint changes only occur if repeated injury is inflicted.

LOOSE BODIES IN JOINTS

Loose bodies in joints vary greatly in their number, nature, and mode of origin. They may be solitary or present in large numbers, even up to 100; they may be composed of cartilage, bone, fibro-fatty tissue, or fibrin; and they may arise as a consequence of either injury or disease. For convenience they may be classified as they occur in healthy or in diseased joints.

Loose Bodies in Healthy Joints. The most striking example of a loose body occurring in a healthy joint is the so-called "classical" loose body in the knee. Such a body is commonly oval in shape and about the size of an almond, and it is almost always single. It results from detachment of a portion of an articular surface, usually a portion

near the posterior aspect of one of the femoral condyles, and consequently one surface of the loose body is usually convex, smooth, shiny and covered by hyaline cartilage, whilst the other surface, originally the deep aspect, is flat or of irregular contour.

Loose bodies of this type almost always affect males in early adult life, and the cause of the detachment is not yet clearly understood. According to Paget, the cause was a "quiet necrosis" of the subjacent bone, presumably resulting from the action of some toxin, and a somewhat similar process has been suggested by Koenig, who gave it the name "osteochondritis dissecans." It seems more probable, however, that the essential feature is thrombosis resulting from trauma, which leads to impairment of the blood supply of a limited area of the articular surface and to slow separation of the devitalized portion. Often there is a history of a previous injury to the joint, and even when such a history is unobtainable there may be presumed to have been a minor injury or perhaps repeated small stresses.

Once set free in the joint such a loose body is apt to become impacted between the articular surfaces and to give rise to pain, locking and effusion of fluid. Subsequently the recurring trauma may predispose to chronic arthritis.

It is an interesting fact that these loose bodies after being set free in the joint continue to live; and indeed the cartilage cells may actually proliferate so that eventually every aspect of the body is covered by cartilage. It appears that the nourishment required for survival and growth is derived from the synovial fluid.

Other loose bodies occurring in normal joints include such bodies as fragments of bone set free by fractures involving joints, and portions of intra-articular cartilages detached by trauma. Loose bodies of both these types most commonly occur in the knee joint, less often at the elbow. The tibial spine may sustain fracture, and the medial semilunar cartilage is often detached, in part or completely, as a result of injury.

Occasionally loose bodies composed of newly formed cartilage derived from the synovial membrane (synovial chondromata) occur in healthy joints, but they are far more common in joints affected by chronic arthritis.

Loose Bodies in Diseased Joints. Loose bodies may occur in many forms of joint disease, but they are most common in tuberculous arthritis, osteo-arthritis and neuropathic arthritis. They occur most frequently in the knee, shoulder and elbow (in that order of frequency), and are rare in other joints.

Fibrinous loose bodies most commonly occur in tuberculous joints. They are small and oval or somewhat elongated, like melon seeds or grains of rice, and they resemble the loose bodies found in bursæ and tendon sheaths affected by tuberculosis. They are of firm consistency but not hard, and consequently they do not tend to become impacted between the articular surfaces. They are usually present in large numbers and there may be as many as a hundred. Occasionally a fibrinous loose body is solitary, and is then apt to attain greater size than the multiple ones.

Microscopic examination shows that the bodies are laminated but

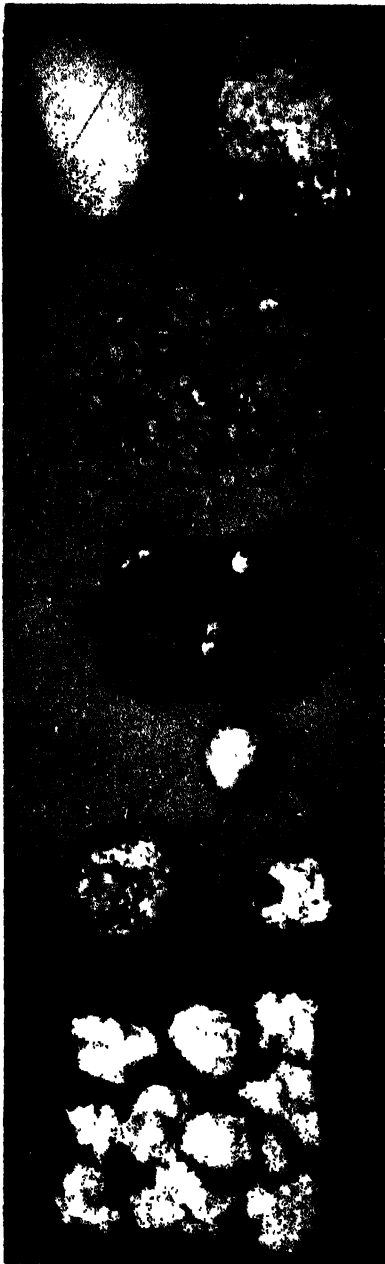


FIG. 102. Loose bodies from joints. (a) A "classical" loose body, with the convex surface smooth, the other rough; (b) multiple fibrinous bodies of melon-seed or rice-grain type; (c) synovial membrane with multiple cartilaginous bodies attached; (d) loose bodies from a case of osteo-arthritis; (e) multiple cartilaginous loose bodies, probably derived from synovial chondromata.

(Department of Surgery, University of Edinburgh.)

have no cellular structure, and they appear to be composed principally of inspissated fibrin. Doubtless they owe their shape to the pill-rolling effect of the joint movements.

Fibro-fatty loose bodies most commonly occur in joints affected by osteo-arthritis or rheumatoid arthritis, but may occur in tuberculous and neuropathic joint disease. They are derived from hypertrophied fringes of synovial membrane, which project into the joint and become polypoidal and pedunculated. Sometimes the bodies lie entirely free in the joint, but more often some remain attached by delicate pedicles. They are liable to become nipped between the articular surfaces and are thus apt to cause recurrent pain and effusion.

Bony and cartilaginous loose bodies are most common in osteo-arthritis, but they may occur in other joint affections.

In osteo-arthritis the marginal outgrowths or chondro-osteophytes may project towards the joint space, and one or more of them may become detached and set free in the joint. Such pathological loose bodies contain small areas of bone but are composed mainly of fibro-cartilage, which serves to distinguish them from separated portions of the articular surfaces, which are composed of hyaline cartilage.

Other chondro-osseous loose bodies are derived from the synovial membrane (synovial chondromata). Many years ago Kölliker showed that the synovial membrane normally contains islets of cartilage cells, and under certain circumstances

these cells proliferate to form cartilaginous masses of considerable size. Such chondromata are usually associated with osteo-arthritis but they may occur in the absence of any obvious joint disease. They may project superficially and be palpable as hard lobulated masses closely related to the articular ends of the bones, or they may protrude into the joint and ultimately be set free. Synovial chondromata are frequently multiple and usually do not attain a diameter of more than a centimetre. Occasionally the greater part of the inner aspect of the synovial membrane is studded with small masses of cartilage. Sometimes there is a single chondroma in relation to an otherwise normal joint, and rarely it may attain large size, for example, the one shown in Fig. 103, which measured 8 cm. in its long axis.

Cysts of the Menisci of the Knee Joint. Cyst formation in the menisci of the knee joint is of fairly frequent occurrence and the lateral meniscus is affected about six times more often than the medial. The cysts involve the anterior third or half of the meniscus and especially its periphery. There may be one or more large cysts which may attain a centimetre in diameter; they are separated by fibro-cartilaginous septa from a variable number of smaller cysts. The cysts contain gelatinous material. The lining membrane is smooth and glistening, and microscopically is found usually to consist of a single layer of flattened cells like endothelium.

The ætiology is not fully understood. In nearly all cases injury has preceded the development of the cysts; and although it may have occurred several months or even years previously, its importance cannot be ignored. But trauma seems to be only an exciting factor, because the cysts lack hæmorrhagic characters. Their clear contents suggest that they may result from degeneration of areas of devitalized fibro-cartilage, probably the result of injury of tissue of normally poor vitality, a belief which is substantiated by the finding of endarteritis in the tissues adjacent to the cysts.

Some regard the cysts as distensions of synovial islet spaces present in the menisci, and assert that the lining is endothelial. The more common belief is that the cellular lining of the cysts is derived from the cells of the cartilage.

Congenital Disc-shaped Lateral Meniscus. The embryonic disc



FIG. 103. Synovial chondroma, measuring 8 cm. in the long axis, removed from the lateral aspect of the knee of a woman aged sixty-two years. The knee joint showed slight osteo-arthritic changes.

(Department of Surgery, University of Edinburgh)

pattern of the lateral meniscus of the knee occasionally persists. In outline it may be circular, quadrilateral, or simply unusually broad at its anterior horn (comma shaped). The importance of the abnormality is that it predisposes the cartilage to injury, and too may be responsible for a peculiar painless snapping noise in the outer part of the knee. The "snap" occurs at about 20° short of full flexion and full extension, and at the same time a momentary check in joint movement occurs and the tibia and femur separate slightly and then fall together again. Both the "snap" and the altered gliding of the joint surfaces are accounted for by the presence of a transverse ridge at the anterior part of the cartilage which in extremes of movement must be surmounted by the femoral condyle.

SPONTANEOUS OR PATHOLOGICAL DISLOCATION OF JOINTS

A joint may be dislocated as a result of disease of the muscles which support it or govern its movements, or from diseases that affect its component parts. In most cases there is a combination of factors, varying in different joints. The joints in which pathological dislocation has been most frequently observed are the hip, the knee, and the occipito-atlantoid articulation.

At the hip pathological dislocation is more common than the traumatic, and the dislocation is always of the dorsal variety. Arthritis, septic or tuberculous, is the commonest predisposing cause, but occasionally paralysis of the abductors and extensors of the hip, such as follows poliomyelitis or birth injuries, has been responsible. Probably in both varieties trauma of such a degree that would not affect a normally constituted joint determines the actual dislocation. The prolonged assumption of the attitude of flexion and adduction, in which position the head of the femur is least supported by the acetabulum, favours dislocation, and the stretched capsular ligaments and eroded articular surfaces render the obstacles still fewer. If the dislocation is overlooked the muscles and ligaments become shortened in adaptation to the altered position of the femur. In old-standing cases the limb is shortened and assumes an attitude of flexion and adduction, and movements are restricted and painful. A false joint may develop on the dorsum ilii above the acetabulum.

Dislocation due to muscular paralysis usually follows the adoption of faulty attitude from unopposed muscle action in paralysis of the abductor and extensor muscles of the hip, or it may follow contraction of the flexor and adductor muscles in spastic paraplegia.

At the knee, spontaneous dislocation is usually due to arthritis, septic, tuberculous or neuropathic. The dislocation is a posterior displacement of the tibia and is attributable to inadequate support of the posterior aspect of the joint whereby the tibia falls backwards out of line with the articular surface of the femur.

Pathological dislocation of the knee is exhibited in an exaggerated form in tabetic arthropathy. From loss of the articular surfaces and

the destruction of intra-articular ligaments the joint may be moved in almost any direction without pain.

At the atlanto-occipital or atlanto-epistrophic joint forward displacement of the skull or of the atlas may occur, as a result of tuberculous caries or from the effects of regional hyperæmia. If the atlas be suddenly displaced forward the dens may impinge on the medulla or the upper part of the spinal cord and cause sudden death. Considerable displacement of the vertebræ may occur without the cord becoming compressed provided the dislocation is gradual. In some cases there is merely torticollis deformity with marked fixation and great pain on attempted movement.

HABITUAL OR RECURRENT DISLOCATION OF JOINTS

Repeated dislocation from comparatively slight causes is especially apt to occur at the shoulder and at the temporo-mandibular joint.

At the shoulder, mobility and wide range of movement are obtained at the expense of stability, and the joint gains relatively slight support from its bony surfaces or capsule, but owes its security principally to the reinforcement of the muscles around it. The glenoid ligament (labrum glenoidale), which consists of a strong ring of dense fibrous tissue, serves to deepen the joint and probably increases its stability.

The usual traumatic dislocation occurs by indirect violence and the head of the humerus escapes through a rupture of the antero-inferior part of the capsule between the tendons of the subscapularis and the triceps. When reduced, sound healing of the capsule occurs and recurrence of dislocation is very unusual. The recurring type of dislocation follows a different kind of injury—an impact from the head of the humerus on the antero-inferior part of the glenoid ligament resulting usually from a fall on the back of the shoulder or on the elbow when the arm is moderately extended. Athletes and epileptics are very commonly the victims of such severe injury. Recurrence of the dislocation, which may occur from very slight violence, is due to shearing off of the glenoid ligament and its failure to reattach itself.

Recurrent dislocation of the temporo-mandibular joint is a relatively rare condition; it may be unilateral or bilateral. The tendency to repeated dislocation has its origin in a former acute dislocation which has produced stretching or rupture of the ligaments and muscles of the joint, and especially the external pterygoid muscle. In some instances the meniscus is unduly lax or is torn, and this predisposes to redislocation.

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CHAPTER X

DISEASES OF MUSCLES, TENDON SHEATHS AND BURSÆ

CONTRACTURE OF MUSCLES

CONTRACTURE of muscles is a frequent accompaniment and sometimes a cause of deformities. The shortening may result from any of the following causes: (1) prenatal lesions of muscle, causing congenital deformity; (2) prolonged approximation of the points of attachment of the muscles, for example, in old dislocations, or after fixation in positions of flexion; (3) weakness or paralysis of opposing muscle groups, for example, in poliomyelitis, or after peripheral nerve injury; (4) disease in the related joint, especially rheumatoid arthritis and gonococcal arthritis; (5) disease or injury of muscles, with subsequent fibrosis and contracture, such as follows fracture or osteomyelitis.

The character of the deformity depends upon the nature and extent of the underlying lesion. Sometimes, especially when resulting from nerve injuries, the deformity is very characteristic, for example, the "main en griffe" of ulnar nerve paralysis and the drop foot following paralysis of its extensor and evertor muscles.

Three special types of muscular contracture—prenatal muscular dystrophy, torticollis, and Volkmann's ischæmic contracture—require special mention.

PRENATAL MUSCULAR DYSTROPHY

Many congenital skeletal deformities, such as *congenital high scapula*, *bilateral club-hand and club-foot* (arthrogryposis multiplex congenita), *congenital genu recurvatum* and *congenital angulation of the tibia*, are now believed to result from muscular dystrophy developing fairly late in intra-uterine life. Recent histological researches in these and other conditions afford suggestive evidence that the underlying defect is some variety of prenatal myodysplasia, in which developing muscles either fail to reach full structural maturity, or, if fully developed, tend to degenerate because they are unable to maintain themselves in a state of high differentiation. No lesion of the peripheral nerves has been discovered.

Congenital high scapula is associated with absence of the lower part of the trapezius, and the upper part together with the rhomboid muscles is the seat of fibrous infiltration. In addition, there is usually evidence of a widespread disturbance of development of the mesodermic structures of the neck, in the form of congenital kyphosis, crania-

spina-bifida, and irregular segmentation of the cervical part of the vertebral column. Probably, as has been suggested by Middleton, the high position of the scapula and its failure to descend are due not so much to muscular anomaly as to irregularity of development of the mesoblastic components of the cervico-dorsal segment of the trunk and the upper limb buds. The muscles of the shoulder girdle merely share in the disturbance of development.

Arthrogryposis multiplex congenita is a rare congenital deformity in which there is bilateral clubbing of the hands and/or of the feet. The muscles of the limbs are wasted and as a result there may be considerable limitation of movement of the joints. When the lower extremity is affected congenital dislocation of the hip joint is frequently present and is of such a type that reduction is more than usually difficult or impossible.

The counterpart of arthrogryposis has been observed frequently in lambs, and is regarded as a simple autosomal recessive. In the human subject hereditary factors appear to be absent. The microscopic appearance of the affected muscles is the same in man and animals and consists of fibro-fatty degeneration, similar to that observed in the muscular dystrophies of later life. Apparently, the muscle degeneration occurs late in intra-uterine life and affects muscle fibres which are already fully differentiated. Once started the degeneration progresses rapidly but ceases at birth.

From the surgical standpoint, it is worthy of note that the club foot differs from the more familiar congenital talipes in that there is absence of muscular power and a greater difficulty in effecting reduction, but after correction there is less tendency to recurrence of deformity.

Congenital genu recurvatum (congenital dislocation of the knee) may be unilateral or bilateral; it is frequently associated with other mal-developments such as club foot and congenital dislocation of the hip. The knee joint is fixed in hyperextension, which can be increased slightly by manipulation; but flexion is restrained by the elastic resistance of the stretched hamstring muscles. Anteriorly the plane of the joint is marked by transverse creases in the skin; posteriorly the prominence of the femoral condyles may be detected. The patella is usually undeveloped or may be absent. The cause of the deformity is contracture of the quadriceps muscle, the result of antenatal fibro-fatty degeneration.

Congenital angulation of the tibia is characterised by anterior kyphotic angulation of the tibia at the junction of its middle and distal third and is associated with extreme and fixed talipes equinus. The limb as a whole is short, particularly the part below the knee. Other abnormalities of development frequently co-exist.

Although there are no demonstrable microscopic changes in the calf muscles, it is thought that the deformity results from failure of the final stages of muscular development, because the finer degrees of muscle dystrophy, short of disintegration, cannot be identified.

The contraction of the affected muscles leads to bending and angulation of the cartilaginous tibia.

CONGENITAL TORTICOLLIS (Wry-neck)

Congenital torticollis results from fibrosis and consequent contracture of the sterno-mastoid muscle. Both sternal and clavicular heads of the sterno-mastoid are affected, and in well-developed cases they stand out as tight bands. The shortening leads to restriction of growth of all the other soft tissues in the affected part of the neck, including the deep fascia, the sheath of the great vessels, and the scalene muscles.

The contracture causes limitation of the movements of rotation and elevation of the head, and the head is flexed, bent towards the affected side, and rotated towards the opposite side. In many cases there is asymmetry of the face and skull; on the affected side the face is small, and the frontal tuberosity is flat; on the opposite side the occipital bone bulges. Owing to excessive shortness of the fibrosed muscle the mastoid process on the affected side is abnormally large, and an exostosis may develop at its clavicular attachment. Thoracic-cervical scoliosis often develops.

No one explanation accounts for the origin of congenital torticollis. In some the deformity is present at birth and must be attributed to developmental aplasia of the affected cervical segments—the usual cause. In others the deformity becomes apparent only when the child is a few years old, when the contracting muscle begins to exert a pull on the growing neck. Such cases develop most often in children after difficult labour, especially after a breech delivery and it is assumed that generally the contracture represents the end-result of a so-called “sterno-mastoid tumour,” a firm, spindle-shaped swelling of the lower half of the sterno-mastoid which sometimes becomes evident a week or two after birth. The “tumour” consists of young fibrous tissue and degenerating muscle fibres. The swelling usually disappears gradually owing to the shrinking of the young fibrous tissue, and the deformity may pass unrecognized until later years.

The mechanism underlying traumatic muscular contracture has been very fully investigated. The “sterno-mastoid tumour” has been attributed to rupture of the muscle during birth or to ischæmia from arterial occlusion, but the investigations of Brooks, repeated and confirmed by Middleton, have suggested that an important factor is obstruction of the venous return from the muscle. Brooks was able to reproduce the condition experimentally in animals, and found that ligature of the artery to a muscle, or of the artery and vein together, produced atrophy but no other changes; whereas, ligature of the veins alone produced the characteristic features of the “sterno-mastoid tumour.” The condition appears to be a hæmorrhagic infarction with fibrous tissue replacement and finally contracture. Since the venous return from the sterno-mastoid muscle is arranged on a segmental plan, injury to one set of vessels cannot be compensated by other vessels; and it is concluded that both the “tumour” and torticollis could follow either rupture or thrombosis of these veins during birth.

VOLKMANN'S ISCHÆMIC CONTRACTURE

This stubborn form of contracture generally affects the flexor muscles of the hand and forearm and causes considerable deformity and disability. Less often (see below) it affects the muscles of the calf and foot. It is an occasional (and sometimes unavoidable) complication of fractures and dislocations in the region of the elbow, less often of more distal fractures. It is commonest between the ages of five and fifteen years, the period when these fractures are most often sustained. In rare instances the contracture has developed after injury to the soft tissues of the arm, the prolonged application of a tourniquet, and embolism of the brachial artery.

At the onset of the contracture, which may be evident a few hours after the injury, there is usually burning pain in the hand and forearm and great agony follows attempts to extend the fingers. Swelling and blueness (rarely pallor) of the fingers are of special significance. The radial pulse is much reduced in volume or imperceptible. When the contracture is fully developed the wrist is flexed, the fingers are extended at the metacarpo-phalangeal joints and flexed at the interphalangeal joints. Since the tendons are free from adhesions the fingers can be straightened after flexing the wrist. The general nutrition of the limb is often impaired, and the hand is cold and blue.

In established cases the appearance of the affected muscles is quite characteristic. They are indurated and surrounded by a dense fibrous sheath, and the muscle substance is replaced by a yellowish-green homogenous substance which cuts with difficulty. The outstanding microscopic change is an irregularly distributed mass-necrosis of muscle fibres with fibrous proliferation around the dead muscle bundles. In places groups of fibres survive and may show hypertrophy.

Volkman's contracture is now known to be due to interference with the arterial blood supply to the muscles. In some cases the brachial artery is compressed directly by a displaced fragment of bone or by external pressure from splints or bandages. In other cases the artery or its branches are obliterated by spasm secondary to the trauma. Yet again they may be compressed by a hæmatoma confined beneath the deep fascia.

Recently it has been shown that a similar contracture may affect the muscles of the calf and foot. If the site of vascular occlusion is the popliteal artery (the result, for example, of pressure by a tight plaster case) all the muscles are involved. More often, a single group of muscles or even a single muscle belly is affected as a result of a less extensive ischæmia due to the pressure of a hæmatoma.

Volkman's contracture is often accompanied by motor and sensory paralysis and was formerly ascribed to nerve injury. It is now clear, however, that while they have a common cause the muscle lesion and the nerve lesion may occur separately and are distinct. The paralysis is due to damage to the main nerve trunks by ischæmia or compression, and eventually it may pass off, whereas the muscle damage is permanent.

RUPTURE OF MUSCLES AND TENDONS

Despite the severe strains to which muscles may be subjected, rupture is not a common injury. Subcutaneous rupture is commonest in adults or elderly subjects following unexpected violent contraction, (sometimes by the opposing group of muscles). Diminished tone or hyaline degeneration, such as may follow a debilitating illness, is sometimes a predisposing factor. The muscle usually ruptures where its fibres converge on tendinous prolongation, but the tear may affect the belly of the muscle or the tendon itself.

The gap created by rupture of a muscle is first filled by blood, then fibrin is deposited, and later granulation tissue bridges the space. Replacement by scar tissue finally occurs, but there is never union of muscle to muscle or regeneration of its fibres, however accurate apposition may have been. The ultimate function of the muscle so far as power and motion are concerned, is likely to be normal provided scar tissue does not bind it to adjacent fixed structures, such as fascia and bone. In some situations the fibrous tissue at the site of repair may become attenuated and, in the abdominal wall, may predispose to hernia.

Severance of a tendon is followed by separation of its ends, and the degree of retraction depends on the position of the part and the state of contraction of the related muscle at the time of the rupture. The process of repair is on the same lines as in muscle by fibrous tissue replacement of the intervening blood clot and fluid exudate. Provided the gap is not excessive, and adhesion of the tendon to adjacent structures can be overcome, the natural process of fibrous contraction effects a secure approximation.

The commonest sites for rupture of muscles (or tendons) are—the rectus femoris, or one or all components of the quadriceps, the tendo-calcaneus, the tendons or muscle bodies of the biceps brachii, and the extensor tendons of the thumb and fingers, especially the index and ring. In rare circumstances the rectus abdominis muscle undergoes rupture, especially below the umbilicus, where its posterior sheath is deficient. Sometimes there is a coincident rupture of the deep epigastric vessels and a diffuse hæmatoma develops. Sometimes the rupture has been caused by direct violence; usually, however, it follows slight exertion, especially in subjects debilitated from such illnesses as typhoid, influenza and pneumonia. It has been observed during pregnancy and parturition and following the muscle cramps of tetanus. The practical importance of the condition is that it simulates intra-abdominal disease such as appendicitis, cholecystitis and strangulated hernia.

OSSIFICATION IN MUSCLES AND TENDONS

Ossification in relation to muscles is usually the outcome of injury, either contusion, fracture, or dislocation. The resulting mass of bone is usually known as *traumatic osteoma*, a designation which justifiably replaces the older term *traumatic myositis ossificans*.

Localized ossification is common in the muscles and tendons of those

subject to osteo-arthritis. The bone is usually in the form of spikes, sometimes known as *false exostoses*, which are often continuous with the roughnesses to which the muscles secure attachment. Similar bone formation may occur in association with neuropathic arthritis, particularly of the knee.

Traumatic Osteoma. A traumatic osteoma resulting from a simple contusion and unassociated with a fracture has been observed most often in connexion with the quadriceps femoris following a severe blow. The bone develops in a hæmatoma and is not usually apparent for five to eight weeks after injury; it is not in the muscle fibres, but between them, or in the inter-muscular planes. If a radiogram of a limb is taken some weeks after a severe contusion it may be noted that, even in the absence of fracture, the bones for a distance from the point of injury show slight rarefaction. It is probable that injury to the periosteum releases lime salts for ossification to occur in the organizing hæmatoma (see p. 115).

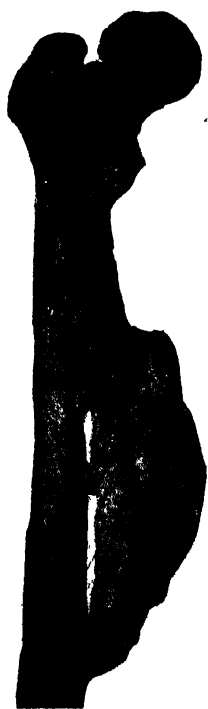


FIG. 104. Traumatic osteoma.

(Museum of Royal College of Surgeons of Edinburgh.)

Intermittent and unaccustomed strain may lead to ossification in the affected muscles or tendons. A familiar example is the keel-shaped plate of bone that grows from the *linea aspera* between the tendons of the adductor longus and brevis in cavalry recruits unaccustomed to horsemanship.

Traumatic osteoma associated with fractures and dislocations has been observed most often in relation to the femur or the humerus, and at the elbow joint. The principles underlying the new bone formation are the same as those mentioned above. At the elbow joint the ossification occurs between the brachialis muscle and the shaft of the humerus, and its occurrence has sometimes been observed after forcible manipulation of a stiff joint; the new bone may lead to considerable limitation of movement, but it tends to disappear provided movement is restricted for sufficient time. If the osteoma persists it may give rise to disability by limiting the movement of the muscles, or by impeding the excursion of a neighbouring joint.

Myositis Ossificans Progressiva. Infiltration of muscles by bone is seen on an extensive scale in myositis ossificans progressiva—a rare disease in which large deposits of lime salts and bone develop in relation to muscles, aponeuroses, ligaments, and fasciæ. It affects young male subjects, seldom women. Its ætiology is not known.

The muscles affected in the early stages are those of the back and neck, especially the latissimus, trapezius, and rhomboids. At the onset of the disease there are attacks of stiffness, swelling, and tenderness in the affected muscles, which become firm and doughy.

Prior to bone formation there is hyperplasia of the intramuscular fibrous tissue and deposition of lime salts between the muscle fibres and in the intermuscular planes. The bone is of a spongy texture and is often disposed in large sheets or plaques in the long axis of the muscles. In addition, there may be large osseous projections from the vertebral spines, the ilia, and the scapulæ. None of the bony masses lies free and unattached to the skeleton.

As ossification progresses, movements of the back and limbs become greatly impaired. The ribs become fixed, and respiration is solely by the diaphragm. Death is due usually to pulmonary infection.

A frequent and striking coincidence in the recorded cases is congenital hallux valgus caused by imperfect development of the phalanges. A similar deformity of the thumbs is usually present.

TUMOURS IN MUSCLES

Tumours in muscles are uncommon, and most of them arise from the muscle sheath or the intermuscular fibrous tissue. The commonest varieties of simple tumour are *lipoma*, *hæmangioma*, and *fibroma*. *Sarcoma* may occur, but is rare.

A **lipoma** may arise in the muscles of the shoulder girdle or of the thigh. In other situations it is rare. The tumour is soft when the muscle is relaxed, but becomes firm and hard during contraction. Difficulty in diagnosis of an intermuscular lipoma may be considerable when it is situated beneath a firm aponeurosis.

A **hæmangioma** is a very rare tumour in muscles. It occurs generally in young subjects, and is probably congenital. The tumour is of the cavernous type, and is localized usually in one part of the affected muscle, but occasionally the tumour is diffuse.

A muscle hæmangioma is usually soft and compressible, unless thrombosis has occurred within it. When the tumour is pulsatile it may resemble a rapidly growing sarcoma.

Fibroma. The only muscle fibroma of importance is that which grows in the abdominal wall. The tumour is of special pathological interest because it has the microscopic characters of a simple tumour, yet it has no capsule, and tends to infiltrate widely, and to recur after removal.

The tumour has been found most often in women following rupture of muscle fibres during parturition, but it may occur as a congenital abnormality in infancy. It is fairly certain that its origin is related to trauma, because in fully 80% of cases it has been found in parous women, and in other instances a history is forthcoming of a blow on the abdominal wall.

When small the tumour is pinkish-white in colour, and is so hard that it creaks when cut. Its cut surface has a tendon-like appearance, hence the old term "desmoid tumour." When large the tumour is softer, and it may show mucoid degeneration. On microscopic examination the tumour has the appearance of a fairly cellular fibroma with cells arranged in bundles or whorls. The stroma is scanty and the blood vessels are small but well formed. A characteristic feature is its

content of muscle fibres, which may be striated and of healthy appearance, or unstriated and with appearances of degeneration.

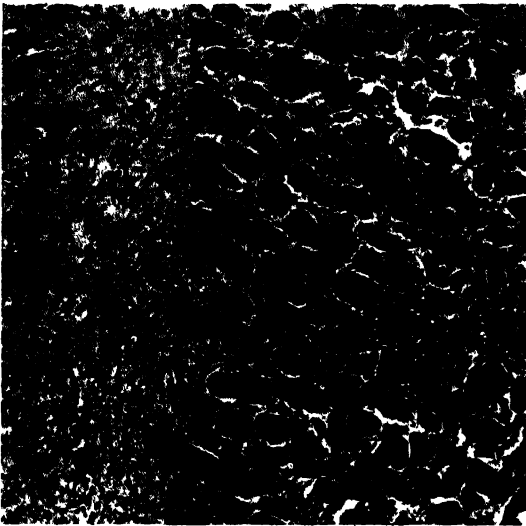


FIG. 105. Fibroma (desmoid tumour) of the rectus sheath. The tumour is very cellular, and has infiltrated between the fibres of the muscle.

(Museum of Royal College of Surgeons, Edinburgh.)

The muscle fibres are probably not an integral part of the tumour, but, according to Stewart and Mouat, are merely isolated and degenerating portions of the infiltrated muscles of the abdominal wall.

The point of origin and the mode of spread of the tumour are fairly constant. Most often it begins in the lower part of the rectus abdominis muscle, less often in the upper part, and very seldom in the external oblique or transversus abdominis. The actual site of origin is

either the muscle sheath or the fibrous tissue between the muscle bundles. As the tumour has no capsule, it has the appearance of infiltrating the muscle substance. On account of the resistance of the rectus sheath the tumour tends to become elongated and assumes a flattened, ovoid shape; its growth is slow, but it may become as much as 25 to 30 cm. in length. For long it remains within the rectus sheath, but it may finally extend to the subcutaneous tissues, or it may adhere to the peritoneum. In the advanced stages it may become adherent to the pubic bones and to the skin. It does not form metastases.

The infiltrating character of the tumour and its tendency to involve the peritoneum may render a very extensive operation necessary for its removal, and recurrence is common unless a very radical extirpation is carried out.

TENOSYNOVITIS

Tendon sheaths have the same structure as the synovial membranes of joints and are affected by the same diseases. They are liable to become inflamed (tenosynovitis) as a result of injury, and to become infected by pyogenic organisms, gonococci, and tubercle bacilli.

Well-developed tendon sheaths are found only at the wrist, in the fingers, and at the ankle joint; and these, therefore, are the usual situations of tenosynovitis.

Traumatic Tenosynovitis. Traumatic tenosynovitis (tenosynovitis

crepitans) sometimes follows a severe strain or excessive use of a particular group of tendons. As only a small number of people who submit their tendons to undue strain develop tenosynovitis, it may be presumed that some constitutional factor must be superadded.

In this variety of tenosynovitis the opposed surfaces of the tendon sheath are covered with fibrinous lymph which imparts a crepitant sensation when the tendons move. It may be accompanied by considerable subcutaneous œdema. There may be an effusion of rusty fluid into the sheath, but it is rarely large in amount. The tendons most often affected are the extensors of the fingers and those of the toes.

Infective Tenosynovitis. Infective tenosynovitis may be of two varieties: (1) acute, and (2) chronic.

(1) **Acute tenosynovitis** may be toxic in origin or due to pyogenic organisms from a septic lesion in the proximity of one of the large tendon sheaths, or to gonococci carried in the blood.

Pyogenic or suppurative tenosynovitis (the cal whitlow) is seen in characteristic form in association with septic infections of the hand. The infection is usually due to streptococci, less often staphylococci. The sheaths of the flexor tendons of the fingers and of the wrist are more often affected than those of the extensor tendons. Infection may arise in any of several ways: not infrequently infection of the sheath follows directly from a prick on the volar surface of the finger, especially at the proximal interphalangeal crease where the sheath is most superficial. In other instances infection is carried by the lymph vessels from an adjacent cellulitis, or it is conveyed from a subcutaneous whitlow either by natural extension or as a result of a careless incision.

When the tendon sheaths of the little finger or the thumb are affected, extension to the common flexor sheath is apt to occur owing to their direct communication with it. In the case of the other fingers such extension is uncommon, for after pus has burst through the proximal end of the sheath, it passes into the middle palmar space or to the thenar space rather than to the common flexor sheath.

When a tendon sheath is infected it becomes hyperæmic and thickened, its inner surface covered with purulent lymph and the sheath distended with pus. If the pus is not evacuated, the tendons, deprived of their blood supply, may slough, and infection may extend to the adjacent bones and joints. The formation of fibrous adhesions usually gives rise to permanent contracture of the fingers.

Gonococcal tenosynovitis may occur as a complication of gonorrhœa in either sex. It may begin at any stage of the infection, but is commonest about the second to the third week of the disease. It has been known to occur in infancy as a result of gonococcal ophthalmia.

Gonococcal tenosynovitis usually occurs simultaneously with infections of the joints. The tendon sheaths at the wrist and ankle are those most often affected, the extensors more often than the flexors.

In the acute stage of the tenosynovitis, gonococci can often be demonstrated in the fluid obtained by puncture of the sheath.

The severity of the tenosynovitis varies. In mild cases there is an effusion of serous fluid into the affected sheath, associated with pain and impairment of movement. In more severe cases there are considerable

redness of the skin and œdema of the subcutaneous tissues. Only rarely does suppuration occur, and if it does the tendons do not tend to slough as in other pyogenic varieties of tenosynovitis. After gonococcal tenosynovitis adhesions may form in the tendon sheath and lead to stiffness.

(2) **Chronic tenosynovitis**, if non-traumatic, is generally tuberculous. The commonest site is the large flexor sheath at the wrist; less often the sheaths of the extensor and peroneal tendons at the ankle joint are involved. The disease affects young adults and is frequently the only manifestation of active tuberculosis (compound palmar ganglion).

The pathological features are observed in most characteristic form at the common flexor sheath at the wrist. Sometimes the extensor and the digital sheaths are affected in addition or independently. The disease may present itself in various forms which are probably accounted for by variations in its duration and by varying local and general resistance. In its simplest and early form a serous exudate is present; later, granulation tissue and "rice bodies" appear; and, finally, in the severer forms extensive caseation may occur.

When inspected at operation the deep fascia is found to be tense and the underlying sheath is no longer white and glistening but yellowish-grey, greyish-red or purple. It is distended with straw-coloured fluid, and the tendons may be thickened and matted together by vascular granulation tissue which renders them dull and lustreless. At a later stage, there may be loculation of the fluid or the sheath may be partially obliterated by fibrous tissue or by "rice bodies." In advanced cases the fluid is replaced by caseous or gelatinous material. At first the tendons, though thickened as a result of proliferation of their visceral sheaths, are healthy; but in severer cases there may be destruction of a single tendon or groups of tendons. The median nerve, which is intimately related to the common flexor sheath, is often swollen as a result of œdema of its sheath, but its fibres are not affected.

The progress of the disease is very variable; in some cases fibrous tissue formation may limit the disease, in others it may assume a chronic hypertrophic form. Sometimes extensive caseation may lead to perforation of the sheath and the development of a cold abscess.

Tuberculous tenosynovitis at the wrist leads to stiffness and weakness of the fingers. Pain of a burning character in the distribution of the median nerve is sometimes present.

Tenosynovitis, when uncomplicated by osseous disease or active lesions elsewhere, is treated most suitably by excision of the diseased tissue, and the degree of recovery depends on the extent to which there may have been destruction of tendons.

Tumours of Tendon Sheaths. Tumours of tendon sheaths are rare. One of the best known is a *simple giant-cell tumour* which grows from the inner aspect of the sheath. It has been found most often in the fingers, at the wrist, or connected with the tendo calcaneus. The tumour, which is yellow or red in colour, grows very slowly, and is rarely larger than a cherry. It is encapsuled and is lobulated in structure. Malignancy of the tumour has not been reported.

Microscopically, such tumours are of variable structure: some are

composed of spindle-shaped cells alone, others contain "foamy" cells like the cells of a xanthoma, and others giant cells of foreign body type. A characteristic feature in many of the tumours is the presence of slit-like "synovial spaces," which are lined with flattened connective tissue cells.

Other tumours of tendon sheaths include chondroma, myxochondroma, fibroma, and, very rarely, sarcoma.

DISEASES OF BURSAE

Bursæ minimise friction, and are usually found where tendons pass over bony surfaces or where the superficial fascia and skin cover a bony prominence. In structure bursæ resemble the synovial capsules of joints and tendon sheaths, of which in some situations bursæ are merely prolongations. At sites where the skin and subcutaneous tissue are exposed to intermittent friction, abnormal bursæ may develop. Such bursæ are known as *adventitious bursæ*, and their development is often due to repeated trauma incident to particular occupations. Similarly, adventitious bursæ may develop in relation to deformities of the skeleton, especially where bony prominences are exposed to abnormal intermittent pressure; familiar examples of such bursæ are those over the head of the first metatarsal in hallux valgus (bunion), those over the tarsus in club foot, and those over the end of the bone in amputation stumps.

Bursæ are liable to many of the same forms of disease as joints and tendon sheaths, and when a bursa is in communication with a joint it participates in any pathological condition that involves the joint.

Traumatic bursitis usually results from excessive friction and pressure, and occurs most often in the superficial bursæ; less often, the more deeply placed bursæ such as the semi-membranosus bursa and the subacromial bursa are affected. Traumatic bursitis is characterized by an increase of serous fluid in the bursa and thickening of its lining membrane. The process may be an acute one, and is then attended by considerable pain and disability. More often, however, the process is chronic, and the bursa distends slowly with fluid (bursal hydrops).

If the inflammation does not subside, or if it relapses frequently, the walls of the bursa may become very thick, and irregular adhesions, septa, or fringes may form in its interior, or concentric thickening may ensue, resulting in a fibrous swelling (*see* Fig. 106). Occasionally, loose bodies of the melon-seed variety may develop within it.

The prepatellar bursa and the olecranon bursa are those most liable to injury, and various fanciful names have been assigned to the conditions according to the occupation which was suspected to produce it, for example, housemaid's knee and student's elbow.

Subacromial bursitis may occur as an immediate or late sequel to injuries to the shoulder, such as a blow, a wrench or a dislocation. In the majority of cases the underlying lesion is an injury, usually rupture, of the fibres of the tendon of the supraspinatus muscle. The rupture

usually takes place close to the greater tuberosity, and the subsequent retraction of the tendon (it may be for as much as $2\frac{1}{2}$ inches) enlarges the gap and establishes a communication between the shoulder joint and the bursa. Probably smaller tears of the tendon, which involve only a few fibres, are quite common, and the intratendinous calcification which frequently follows may give rise to the features of traumatic subacromial bursitis.

Acute infective bursitis frequently follows abrasions and wounds, and, as superficial bursæ are structurally related to the lymph vascular



FIG. 106. Bilateral chronic prepatellar bursitis in a woman aged eighty-three; *above*, concentric thickening due to proliferation of fibrous tissue; *below*, large swelling due to fibrous tissue overgrowth and gelatinous degeneration.

system, it is not uncommon in cellulitis or lymphangitis. The prepatellar and the olecranon bursæ are most often affected.

In suppurative bursitis the walls of the bursa become greatly thickened, the inner surface is destroyed, and the cavity is filled with thick yellow or sanious pus. The resulting abscess may burst through the skin or track for a considerable distance in the subcutaneous tissue and lead to cellulitis. When healing occurs the bursa may be completely obliterated by fibrosis.

Gonococcal bursitis is less common than gonococcal arthritis, which it resembles very closely in its pathological features. The bursa most often affected is that at the insertion of the tendo calcaneus.

Tuberculous bursitis is uncommon. It is most apt to occur in bursæ near large joints, such as the hip, shoulder and knee, and is then usually secondary to tuberculosis of these joints. Nevertheless the subacromial bursa, which does not normally communicate with any

joint, may be the seat of tuberculosis in the absence of disease in the neighbouring bones or joint. Similarly, the ilio-psoas bursa, situated between the psoas muscle and the capsule of the hip joint, may be affected by tubercle, as may the various bursæ related to the glutea muscles.

Other Diseases of Bursæ. In gouty subjects chalk may be deposited in the walls of bursæ. Calcareous deposits in the subacromial bursa or in the tendon of the supraspinatus muscle are common and are usually the result of trauma. Involvement in syphilis is extremely rare.

The occurrence of a giant-cell tumour, fibroma, and myxoma in bursa has also been reported.

Ganglion. A ganglion is a cystic swelling which occurs in the neighbourhood of a joint or tendon sheath, especially at the wrist, ankle, and knee. In many instances it appears soon after a strain, in others there is no obvious cause. Ganglion is common in either sex, but more so in women than in men. Often it disappears spontaneously.

The cyst is generally unilocular, is very thin walled, and contains clear, jelly-like fluid. It may reach the size of a pigeon's egg. The wall of the cyst is composed of fibrous tissue which adheres lightly to the surrounding tissues. There is no endothelial lining. The mode of origin of a ganglion is uncertain. It is generally stated that it arises from a synovial sheath or a joint. Certainly at the carpus it is usually possible to demonstrate a communication between the ganglion and the interior of the wrist or intercarpal joints. Although the cyst may adhere to the tendon sheaths, a communication with them is not usually discovered.

The most likely cause of ganglion formation is mucoid degeneration of injured capsular ligaments; in some instances they may be extrusions of synovial membrane from nearby joints.

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CHAPTER XI

DISEASES OF BLOOD VESSELS

PHLEBITIS (THROMBOPHLEBITIS)

ACUTE phlebitis may occur as an independent condition or in association with inflammatory lesions. It may arise in local or generalized affections or in the absence of any recognizable cause, and it may occur as an aseptic process or as a result of organisms of various degrees of virulence. In the more severe forms, suppuration occurs in and around the vessel wall and within the contained thrombus.

For convenience, the following forms of phlebitis may be recognized : (1) Phlebitis due to trauma. (2) Phlebitis due to toxic substances either present in the circulation or injected therapeutically. (3) Phlebitis due to infection from either a local or distant source. (4) Phlebitis of undetermined origin.

(1) **Phlebitis due to Trauma.** Inflammatory change in the wall of a vein is a necessary accompaniment of any severe trauma, but unless complicated by infection it almost invariably remains localized to the seat of injury. (Sometimes, especially in elderly subjects, a slight trauma may determine the onset of extensive phlebitis, particularly in veins of the leg or thigh, and these vessels may then become thrombosed, and, if superficial, may be obvious as firm, tender cords.) It seems likely that in such cases there is generally a second factor such as a mild infection or pre-existing degenerative change in the vessel wall. It is commonest on the right side and in young subjects.

In rare instances thrombosis may occur suddenly in the axillary vein following unusual muscular strain. The underlying cause would appear to be overstretching and contusion of the vessel between the clavicle and the first rib and the costo-coracoid membrane and the subclavius muscle.

(2) **Phlebitis due to Toxic Substances.** Phlebitis occurs not uncommonly in the course of chronic disease characterized by grave toxæmia, anæmia or cachexia, and it may be presumed to result from the action of toxins upon the endothelial lining of the veins. It sometimes develops in the splenic vein in the later stages of splenic anæmia. Phlebitis may result also from the action of therapeutic substances injected intravenously, especially if the drug is injected rapidly or in too concentrated solution. (The production of aseptic phlebitis is the aim of the injection treatment of varicose veins and of hæmorrhoids.)

(3) **Phlebitis due to Infection.** Veins are necessarily involved to some extent in all inflammatory conditions of the tissues they traverse, and since the veins have thin walls and a sluggish blood flow, they are much more liable to infection than arteries. In most cases infection is preceded by thrombosis and by reactive proliferation of endothelium and young fibrous tissue in the vessel wall, which prevent access of

organisms to the blood stream ; but if the infection is rapid and virulent the newly formed blood clot in the lumen may suppurate, soften, and form emboli, which may give rise to grave and often fatal pyæmia.

Suppurative phlebitis most frequently involves the lateral intracranial sinus, as a result of infection from the middle ear (*see* p. 573). The facial and orbital veins may be infected from septic processes on the lips and cheek, the uterine veins may be infected from endometritis (*see* p. 680), the portal vein and its branches from appendicitis (*see* p. 547).

Another form of infective phlebitis occurs during or subsequent to acute infections such as pneumonia or typhoid fever. The phlebitis most commonly affects the deep veins of the left lower extremity. It may give rise to a severe and prolonged constitutional reaction but suppuration rarely follows, and embolism does not commonly occur.

(4) **Phlebitis of Undetermined Origin.** Not infrequently phlebitis occurs in otherwise healthy subjects without obvious cause. It is especially apt to affect elderly persons, and occurs usually in varicose veins or in situations where the blood is apt to stagnate. For this reason the lower limbs are commonly affected. It seems probable that in these cases phlebitis arises upon a basis of several contributory causes, including stagnation of the blood, disease of the vessel wall, trauma and mild infection.

Post-operative Phlebitis. This is a most important form of the disease. It may follow any type of operation, but is especially common after operations upon the abdomen or pelvis. It is most frequent in old persons, but is by no means unknown in young and healthy subjects. Phlebitis of a similar type may occur after childbirth. In the great majority of cases the phlebitis occurs either in the immediate neighbourhood of the operation wound or in the veins of the lower extremity, and in the latter case the left side is affected three times more commonly than the right. This incidence on the left side is to be explained by the fact that the left common iliac vein is crossed near its termination by the origin of the right common iliac artery, and is thereby constricted, with consequent slight stasis of the blood.

Post-operative phlebitis may be limited to the small superficial veins of the calf, it may affect the greater part of the saphenous system, or it may extend to the principal deep veins of the limb. Not uncommonly it involves the pelvic veins and the left iliac vein as far as the crossing of the right common iliac artery. If extensive, the phlebitis leads to œdema and swelling of the limb, with blueness or pallor of the skin (*phlegmasia alba dolens*). Since venous obstruction alone gives rise to no œdema (at least in young active subjects), it is presumed that in such cases periphlebitis has led to inflammation and obstruction of the lymph channels too.

The great danger of the condition lies in the liability of the clot to soften, and the consequent occurrence of pulmonary embolism (*see* p. 337). It is noteworthy that this complication seems much more apt to supervene upon a small unnoticed phlebitis of a deep-seated vein than upon a widespread phlebitis in which the whole limb is swollen, probably because the latter condition precludes movement.

The cause of post-operative phlebitis is not clearly understood, but it seems probable that there are several contributory factors. The most clearly defined of these factors are (1) stagnation of the blood resulting from a constrained position during the operation or from reduction of the blood pressure during or after operation; (2) the presence in the blood stream of tissue products set free at the wound or by traumatization of muscles; (3) the occurrence of mild infection.

ANEURYSM

An aneurysm has been defined as "a space or sac formed by the widening or extension of the lumen of an artery, and thus containing blood or clot." It is customary to recognize *true aneurysms*, resulting from disease and bounded by the stretched-out coats of the arterial wall, and *false or traumatic aneurysms*, resulting from puncture or rupture of the artery, and bounded only by condensed fibrous tissue derived from adjacent structures. There is, however, no essential difference in the morbid anatomy of the two forms, for in true aneurysms of any considerable size the sac wall rarely contains any trace of the original coats of the artery.

The predisposing cause of an aneurysm is weakening of the arterial wall, especially of its middle coat of muscle and elastic fibres, which stretches and eventually gives way under the pressure of the blood. High blood pressure is an important contributory cause, but is not a necessary one. The weakening of the arterial wall may result from developmental defects, disease or injury. Amongst diseases predisposing to aneurysm, syphilis stands foremost, because of its especial tendency to affect the middle arterial coat. Simple atheroma and arterio-sclerosis are of less importance. In some situations weakening of the media results from a chronic peri-arterial infection, as, for example, in arteries traversing tuberculous cavities or large peptic ulcers.)

An aneurysm may be fusiform or saccular. In the saccular type the communication between artery and aneurysm may be small at first, but as the sac increases in size the adjacent and opposite arterial wall expands so that eventually there is a large cavity in which the afferent and efferent limbs of the artery may be far apart. Branches of the artery become involved by the enlarging sac, and, separated from their parent trunk, lead directly from the aneurysm, so that finally the aneurysm communicates freely with a considerable number of vessels. For this reason there is a great liability to recurrence after proximal ligation of the main trunk alone. The interior of the aneurysm is rough and irregular, and on it consequently the blood tends to clot. When coagulation occurs intermittently, there is a formation of laminæ of various ages, the older being pale and fibrous, the more recent red and jelly-like.

Traumatic Aneurysm. Trauma may determine the onset of an aneurysm of a diseased artery, but the term "traumatic aneurysm" is restricted to those cases in which a healthy artery is affected. The trauma is usually from penetrating bullet wounds or stab wounds,

but occasionally from puncture by a spicule of fractured bone. Traumatic aneurysm is apt to follow lateral or traversing wounds of arteries, particularly when the wound is oblique and the entrance and exit wounds small or valvular. It never follows complete severance of an artery, an injury which permits retraction of the muscular coat and closure of the arterial wound. The arteries of the neck and extremities are commonly affected, especially the carotid, axillary and femoral arteries.

The extravasated blood at first forms a simple hæmatoma in the peri-arterial tissues, but within a short time it becomes circumscribed and surrounded by fibrous tissue, which forms a recognizable sac, sometimes partly lined by endothelium derived from the arterial intima.

In about half the cases, there is a coincident wound of the accompanying vein, and this is followed immediately or subsequently by the establishment of a communication between the two vessels (arterio-venous aneurysm). Usually the artery and vein communicate directly or by means of a short wide channel (aneurysmal varix); less often the anastomosis is indirect, through an intervening sac lying in the soft tissues (varicose aneurysm). Such an intervening sac is often of irregular shape and very tortuous, and, from the pressure of the blood within, it is apt to enlarge progressively.

In the days of venesection arterio-venous aneurysms frequently occurred in the cubital fossa. Nowadays, they are usually due to bullet wounds, and consequently in Great Britain are very rare. Occasionally an arterio-venous aneurysm occurs in the intracranial portion of the internal carotid artery following fracture of the base of the skull, and gives rise to the condition of pulsating exophthalmos (see p. 234).

Arterio-venous aneurysms provide an interesting illustration of the adaptation of structure to function. There is a great increase in the blood flow through the artery proximal to the anastomosis, and a great decrease in the blood flow through the artery distal to it. Consequently the proximal part of the artery dilates, the distal part becomes contracted. The vein, suddenly subjected to pressure greatly in excess of normal, becomes greatly dilated and tortuous, and since the pressure is not sustained but rhythmically alternating, the wall of the vein undergoes hypertrophy and often attains the thickness of an artery. Proximally, the dilatation may extend even as far as the vena cava and the heart (which is hypertrophied); distally, it is checked temporarily by any valve present in the vein, but later it renders the valve incompetent and extends distally. If the fistulous communication is occluded temporarily the heart beat is notably slowed and the pulse pressure rises sharply (the so-called bradycardia phenomenon).

Congenital Arterio-Venous Fistula. In rare instances, as a congenital defect, there are communications, usually multiple, between arteries and veins. The vessels most commonly affected are those of the extremities, the fingers, and the brain. Even the vessels within bone may be involved.

Sometimes the defect is obvious at birth, but quite frequently the arterio-venous communication is not established until adult life and

then often following a strain. The condition may lead to overgrowth of the part affected or the reverse ; or, when the communications are diffuse, to the impression of a rapidly growing tumour. When the limbs are affected gangrene develops in a large proportion of cases as a result of diversion of arterial blood *via* the veins.

Aneurysms at Special Sites

Aneurysm of the Thoracic Aorta. This is by far the commonest example of aneurysm. It is of surgical interest principally from its pressure effects and from its tendency to mimic other intrathoracic lesions. Pressure upon the œsophagus may lead to dysphagia and mimicry of œsophageal carcinoma. Pressure upon the bronchi may simulate bronchial carcinoma. Pressure upon either of these structures and upon nerves and veins may lead to the suspicion of a mediastinal tumour, and the differential diagnosis, especially in the absence of a positive Wassermann reaction, may be very difficult.

Aneurysm of the Abdominal Part of the Aorta. An aneurysm in this situation is of interest because it may simulate many forms of intra-abdominal disease. The aneurysm, commonest in women, is situated usually in the upper part of the abdomen, and it is apt to extend to one side or the other in the perinephric tissues, causing pressure upon adjacent structures and leading to pain similar to the pain of renal or gastric disease. Sometimes such an aneurysm leaks into the smaller peritoneal sac, which becomes filled with blood clot and gives rise to a large immobile swelling. At the time of such leakage, or subsequently when the blood percolates through the epiploic foramen (foramen of Winslow) to reach the general cavity, the aneurysm may give rise to fatal intraperitoneal hæmorrhage.

Aneurysm of any part of the descending aorta may extend posteriorly and cause erosion of the vertebral bodies. It is an oft-quoted observation that in these circumstances, although the bone is extensively destroyed the intervening fibro-cartilage remains almost intact.

Aneurysm of the Popliteal Artery. This was formerly a common condition, but is now extremely rare. Syphilitic arteritis was the usual underlying cause. It occurred principally in postboys and others accustomed to much riding, and it has been suggested that the S-shaped bend of the artery caused by prolonged flexion of the leg on horse back, and pressure of heavy riding boots in the popliteal space, were aggravating factors. The surgical importance of the condition arises from the inadequacy of collateral circulation around the knee, and the consequent liability to gangrene of the extremity.

Aneurysm of the Palmar Arteries. An aneurysm may develop in any of the component trunks of the superficial or deep palmar arches. A traversing wound may determine the development of the aneurysm, especially in the ulnar artery. In some cases the aneurysm follows a single severe blow on the palm of the hand ; in others it results from repeated minor trauma, such as may be sustained in laborious manual occupations. Aneurysms of the palmar arteries are seldom larger than a pea, but, from pressure, they may give rise to considerable pain.

Aneurysm of the Cerebral Arteries. At post-mortem examination in adults it is common to find small saccular aneurysms of the cerebral arteries. They are of developmental origin and are present most often in the component trunks of the *circulus arteriosus*, especially on the left side. In size they vary from a large pin's head to a grape. They arise very constantly at the junction of the basal cerebral



FIG. 107. Aneurysms of the cerebral arteries. Three aneurysms are seen on the middle cerebral arteries and the anterior communicating artery respectively. Death resulted from hæmorrhage from the anterior aneurysm.

(By courtesy of Prof. J. W. S. Blacklock.)

arteries with their branches or with the internal carotid artery. The commonest sites are the junction of the posterior communicating branch with the internal carotid, the point of bifurcation of the carotid into anterior and middle cerebral arteries, and the point of origin of the first large branch of the middle cerebral artery in the lateral fissure. Less often an aneurysm may arise at the origin of the ophthalmic artery, or at the origin of the anterior communicating artery. The basilar and vertebral arteries are seldom affected.

Aneurysms of the basal cerebral arteries occur in quite young subjects and even in childhood. Arteriosclerosis and syphilis take no part in their development. The adventitial and the muscular coat of the cerebral vessels are poorly developed, and local defects in the vessel walls are common, so that even with a normal blood pressure dilatation may occur.

An aneurysm of one of the cerebral arteries may produce no effects, but rupture, leading to subarachnoid hæmorrhage is relatively common.

Its occurrence in otherwise healthy subjects under thirty years is well known. Rupture may be fatal, but more often the extravasation is localized and is associated with severe frontal headache and an incomplete paralysis of the oculo-motor nerve. When the extravasation is more widespread the signs are those of cerebral hæmorrhage, usually followed by cranial nerve palsies and focal cerebral signs. In a few instances an aneurysm may reach a large size and produce local pressure effects similar to those caused by an intracranial tumour.

Aneurysm of the intracranial part of the carotid artery as it traverses the cavernous sinus is fairly common, especially in middle-aged women. It is usually of saccular type and most often involves the anterior extremity of the vessel. In rare cases the condition is bilateral. The usual causes of arterial degeneration do not contribute to the formation of an aneurysm at this site.

The limitations of space within the cavernous sinus and the proximity of the nerve trunks which it harbours in its lateral wall, account for the somewhat dramatic onset of symptoms and the sequence of paralytic phenomena. The onset, more often abrupt than gradual, is attended by bursting neuralgic pain over one side of the head and in the eye, followed by a varying degree of ocular muscle paralysis. One or more of the branches of the semilunar ganglion—commonly the first and second—show pressure effects. The initial explosive effects are usually followed by a gradual subsidence, but significant pressure phenomena persist. In rare instances, when there has been stripping of the dura mater from the middle fossa, there may be paresis of the facial nerve or even pressure on the brain stem. In established cases there may be deformation of the surrounding bone, particularly of the sphenoidal boundaries of the orbital fissure, the optic foramen and the anterior clinoid process. Concentric rings of calcification within the aneurysm are sometimes present.

Intracranial Arterio-venous Fistula of the internal carotid artery within the skull is due in most cases to injury, but it may arise spontaneously from rupture of a simple aneurysm into the cavernous sinus.

A large proportion of fractures of the base of the skull involve the body and the greater wing of the sphenoid, so that it is not surprising that the carotid artery, which is relatively fixed in the cavernous sinus, is sometimes injured. On rare occasions the artery has been injured directly by a traversing wound of the orbit. The wall of the artery may be torn at the time of the accident, or its coats may be so damaged that a communication with the sinus develops later. The nerves in the cavernous sinus may be damaged at the time of the accident or be submitted to pressure later.

The objective features of an arterio-venous aneurysm resemble those of a simple aneurysm, but, in addition, it is characteristic that the orbital and palpebral veins become dilated and "arterialized," so that pulsation may be seen in them. The eyelids often become coarse, thick, and cyanotic. Pulsation and protrusion of the eyeball is often present—*pulsating exophthalmos*. The patient is usually conscious of a continuous bruit which is very disturbing, especially at night. There is usually a notable deterioration in general health.

TUMOURS OF BLOOD VESSELS ; HÆMANGIOMA

A hæmangioma is the commonest tumour of childhood. It is often present at birth or becomes evident soon afterwards, and is rare in adult life except in the form of minute lesions in the skin of the abdomen and thorax (de Morgan's spots). The tumours are often multiple and vary in size from a tiny red or purple speck in the skin to a tumour which covers the whole face or a large part of a limb. The tumours most often involve the skin, but may be entirely subcutaneous. Less commonly they are found in the liver, the lung, or in the mucous membranes of the mouth, larynx or alimentary tract. Rarely they arise in the bladder or the renal pelvis and sometimes in the bones of the skull and the vertebræ. Angiomatous tissue is a common constituent of teratoid tumours.

The ætiology of hæmangioma has aroused considerable dispute. The various stages in blood vessel development provide abundant opportunity for the production of anomalies, so that probably all types are not alike in their origin. Those met with in childhood are of congenital origin and are believed to develop from angioblastic tissue that has not established its normal connexion with the circulatory channels. The blood corpuscles within the nævus must come from the general circulation ; though the tumour does not have a close connexion with vessels of the adjacent tissues, it has its own supporting vessels (evidenced by injection experiment). Others, such as the "spider nævus," are probably in many instances due to localized dilatation of capillaries and therefore have a connexion with the vascular system. The familiar vascular telangiectasis seen on the legs or on the face is probably an exaggerated example of such a simple dilatation.

Fraser classed hæmangiomata into three histological types : (1) the capillary, (2) the compact, and (3) the cavernous. This classification is preferable to the older ones which grouped the tumours either according to the position they occupied relative to the skin (cutaneous, subcutaneous, and mixed), or according to their colour (capillary, arterial, and venous).

A capillary hæmangioma may take any of several different forms. It is often present as a superficial blue or pink staining of the skin of the face—popularly known as a mother's mark or port-wine stain. The affected area may be small, or it may involve almost the entire face. In the limbs or the trunk it may cover a wide surface or have a patchy or mottled distribution. In other instances, and especially in babies, the tumour appears as a bright red swelling slightly raised above the surface of the skin. The tumour is usually small and circular and looks like a raspberry, or it may have a linear outline. When the tumours are multiple they may roughly conform to the distribution of one of the cutaneous nerves.

The "spider nævus" or nævus araneus appears as an aggregation of dilated and tortuous capillaries on the face or hands. This type is probably not a true tumour but merely a dilation of some of the cutaneous arterioles.

Microscopically, a capillary angioma is composed of a mesh-work

of endothelium-lined, irregular channels of variable size containing a few degenerated red blood corpuscles. The endothelium is supported by a delicate reticulum of areolar tissue which contains fine blood vessels, but the blood vessels do not normally communicate with the endothelial spaces of the tumour. The epidermis over the tumour is thin and delicate, and may be pigmented.

A compact hæmangioma is believed to be derived from a capillary hæmangioma whose cells have undergone massive proliferation. It is usually situated in the subcutaneous tissues and is solid or partly cystic. The skin is often slightly raised and thinned over the tumour, so that it presents a bluish tinge. The tumour possesses a thin capsule, and on histological examination is found to consist of solid alveolar masses of round or cubical cells in which no trace of lumen is evident.

A cavernous hæmangioma consists of a number of blood spaces which intercommunicate. The spongy network of the tumour occu-

pies not only the skin itself, but the subcutaneous or submucous tissues. A primitive type of endothelium lines the vascular channels. The tumour is usually present at birth and has a dark red or purple colour and irregular surface; it is often present about the head and face, especially the lips and buccal cavity. During the early months of life it may extend and infiltrate rapidly, and ulceration of its surface may lead to severe hæmorrhage.

A cavernous hæmangioma may arise

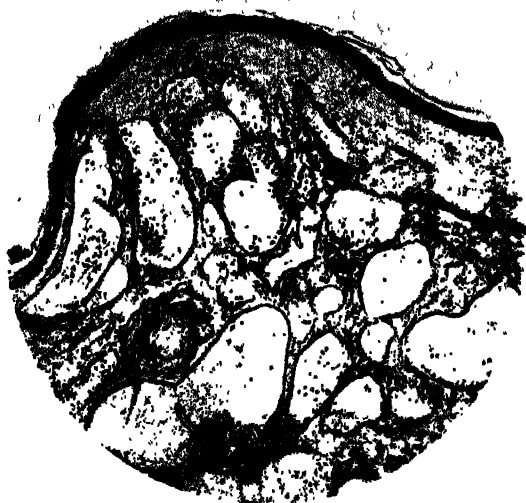


FIG. 108. Capillary hæmangioma of skin. Note the endothelium-lined spaces containing scanty degenerate red blood corpuscles.

(Laboratory of Royal College of Physicians of Edinburgh.)

primarily in bones, especially those of the skull, which may radiographically assume a honeycomb appearance.)

Usually a hæmangioma is an innocent tumour, and it is characteristic of it that it tends to regress. This change is often observed at the first dentition, at puberty, or after an acute illness. But there are instances in which a hæmangioma has assumed malignant characters and has given rise to metastases in the lungs, with death from hæmorrhage or anæmia.

The surgical treatment of a large hæmangioma may present great difficulties, especially when it occurs on the face and involves the eyelids, the lips and the tongue. In these situations elaborate plastic

procedures may be required to reconstruct the features after excision of the tumours. Radium must be employed with great care in the large capillary and the cavernous type on account of the necrosis, telangiectasis or pigmentation of the skin that it may produce. (The cells of the cavernous type are very radiosensitive.)

Malignant Hæmangioblastoma (hæmangio-endothelioma). Sometimes a hæmangioma presents malignant features from the outset. Such a tumour may assume large proportions and metastasize by both the lymph and blood vessels. It has developed most often in the liver



FIG. 109. Angioma of the lip. The tumour was of dark blue colour, and projected under the mucous membrane and skin of the lip.

(Museum of Royal College of Surgeons of Edinburgh.)

(which may be cirrhotic), the spleen, the lungs, and the retroperitoneal tissues.

Arterial Angioma : Cirroid or Racemose Aneurysm. This rare condition may arise in infancy or in adult life. It consists of an overgrowth of small arteries, which are intertwined in racemose fashion. The arteries pulsate visibly, giving an appearance likened by Virchow to a pulsating mass of earthworms. The veins and capillaries may be increased in number. It is not clear whether the condition is to be regarded as a true tumour of blood vessels or as a simple dilatation arising on a basis of a congenital anomaly.

In the great majority of cases a cirroid aneurysm affects the side of the scalp, and it tends to spread over the head and also to the upper part of the neck. The great vascularity of the growth induces decalcification of the skull and may eventually perforate it.

VASCULAR OBLITERATIVE DISEASES

The blood vessels of the extremities may undergo gradual obliteration as a result of organic diseases, such as arteriosclerosis, atheroma and thrombo-angitis obliterans; they may be occluded suddenly by embolism or thrombosis; or they may undergo recurrent constriction in such vasospastic disorders as Raynaud's disease. The pathological results of these occlusions are of profound significance in the recognition and treatment of the vascular disorders of the limbs.

The effects of circulatory arrest may be studied in patients suffering from arterial disease, or, more conveniently, in normal subjects after the application of a tourniquet or an inflatable cuff to the limb. In the latter field particularly the work of Lewis and his colleagues stands pre-eminent.

Discoloration of the Skin. When an inflatable cuff is applied, and the pressure raised above the systolic blood pressure, the first objective change is in the colour of the skin, which first becomes deathly pale, then congested and cyanotic, and finally mottled.

The early pallor is due to draining of the blood from the skin capillaries into the more deeply placed veins, as can be shown by microscopic examination of the nail-beds.

The congestion and cyanosis appear within a few minutes and gradually deepen. They are due to regurgitation of the blood, now deprived of its oxygen content, into the superficial capillaries, which have undergone dilatation as a result of the direct action on their lining endothelium of vasodilator products of metabolism, pent up in the adjoining tissue spaces.

The mottling of the skin is an interesting but unexplained phenomenon, which comes on gradually and is persistent. It consists of white areas, "Bier's spots," with intervening zones of cyanosis, and is to be regarded as due to local vascular constrictions of unknown origin.

Temperature of the Limb. Clinical records often suggest that in a sudden vascular occlusion the limb rapidly becomes "stone-cold." It is obvious, however, that the loss of heat must be a gradual process, and Lewis's observations indicate that a considerable time elapses before the limb reaches room temperature. Cooling takes place most rapidly in the distal part of the extremity, and the tips of the fingers approximate to room temperature in about half an hour. The proximal part of the limb takes several hours to cool to this extent.

Effect on Nerves. The nerves of the limb lose their function with some rapidity under ischaemic conditions. Within 15 minutes of a complete circulatory arrest there is numbness at the finger tips, and from this time on there is a gradual spread of sensory and motor paralysis up the limb. The paralysis is a temporary one, however, and recovers within a few minutes after release of the tourniquet, though there may be some persistent weakness from direct pressure upon the nerves.

Effect on Muscles. If the muscles of the ischaemic limb are contracted vigorously, severe pain is caused, owing, it is thought, to accumulation within the muscle of the products of activity which

should normally be carried away in the venous blood. The pain is of cramp-like character, a diffuse, continuous ache, felt in the muscles themselves, and very severe. It disappears rapidly after release of the tourniquet. This pain is similar in character to the pain of intermittent claudication, seen in many cases of vascular obliteration, *e.g.*, in arteriosclerosis. The pain comes on early in complete arterial obstruction, more slowly if the blockage is incomplete, and it thus forms a reliable index to the extent of the disease.

Effect on Collateral Circulation. If the main artery to a limb is obstructed, the fate of the limb depends upon the extent to which the collateral circulation can be developed. The development of a collateral circulation is not so simple a process as might be imagined. The older view that the blood, denied entrance to the main artery, forced its way under an increased pressure along smaller channels, is no longer tenable. Indeed, the pressure proximal to the block is not increased but, on the contrary, lowered, with the result that the lumen of the artery between the block and the nearest collateral vessel proximally becomes reduced.

It seems likely that the immediate stimulus to the formation of a collateral circulation is the result of lowered blood pressure within the ischæmic territory. In addition the vessels within the ischæmic territory become dilated as a result of the accumulation of vasodilator metabolites from the tissues, resulting in a diminished resistance to the blood flow along the collateral channels. The collateral vessels undergo dilatation and compensatory hypertrophy, and the blood flow to the extremity may finally be restored to its normal volume.

The extent of the collateral circulation, and the rapidity with which it can be opened, depend upon a number of factors, and especially upon the character of the obstructing agent and upon the condition of health of the collateral channels. If the obstructing agent is a simple ligature, the minimum amount of clotting occurs in the vessel proximal and distal to it, and all available collaterals can be utilized. On the other hand, if the obstruction is caused by thrombosis in an arteriosclerotic artery, or even by an embolus, it is sometimes found that several collateral channels are obstructed owing to spread of thrombosis within the main artery. The condition of the collateral channels has an obvious importance; if healthy, they undergo considerable dilatation under the influence of the vasodilator products, whereas if diseased they may be quite incapable of dilatation. The estimation of these potentialities is of outstanding importance in the treatment of disorders of the circulation.

Tests of Vascular Obliteration. In severe cases the presence of vascular impairment is obvious. The limb is generally colder than its fellow, pale or cyanotic; the pulse is diminished or absent; the vessels may be palpably thickened; signs of gangrene may be evident.

For less marked cases, and in order to estimate the degree of impairment, the following tests may be carried out:—

(1) *Pulsation of Peripheral Vessels.* In the lower limbs pulsation may normally be felt in the femoral artery at and below the groin, in the popliteal artery, in the posterior tibial artery behind the medial malleolus, and in the dorsalis pedis artery at the ankle. In vascular

disease the pulsation is lost in the reverse order. Absence of pulsation does not necessarily signify that the vessel is obliterated; there may be a continuous flow of blood, non-pulsatile due to blocking of the main vessel proximally. In borderline cases pulsation may return if the peripheral vessels are dilated by warmth; this may be effected by warming the limb, or, better, by applying heat to the trunk so as to warm the arterial blood going to the limb; pulsation may also return during pyrexia.

To test for the presence of pulsation in a doubtful case an oscillometer may be used. This is a cuff applied to the part to be tested, inflated and connected with an aneroid manometer. Oscillations similar to those observed during blood pressure estimations are demonstrated, and may be recorded graphically.

(2) *Skin Temperature Tests.* The skin of the affected limb should be compared with its fellow (*a*) as the two limbs lie in bed; (*b*) after exposure for a few minutes to the cold air; (*c*) after immersion for a few minutes in water at body temperature. The skin temperature may be gauged with fair accuracy by touch, preferably using the back of the fingers; or special skin thermometers or thermo-electric couples may be used for exact records. (In a limb of impaired vascularity the temperature is normal when the limb is protected by bedclothes, but cools more rapidly on exposure and warms less rapidly when heated.)

(3) *Elevation of the Limb.* If the two limbs, thoroughly warmed to eliminate spasmodic vasoconstriction, are raised above the level of the body, say to 45 degrees, the limb with diminished vascularity becomes deathly pale. For purposes of comparison, the level at which this sign develops may be recorded.

(4) *Tests of Vasodilatation.* Normally all the vessels of a limb are in a state of tonic vasoconstriction. When the main vessels are obliterated by disease, the nutrition of the extremity depends upon the degree to which the collateral vessels can dilate. If the collateral vessels are healthy, improvement may be effected if the vasomotor control can be abolished by paralysing the sympathetic innervation; if, on the other hand, they are diseased, little or no improvement can be expected.

To assess the benefit to be anticipated from sympathetic denervation, the vasomotor control may be abolished temporarily in the upper limb by anæsthetizing the cervico-dorsal sympathetic trunk with novocain, or in the lower limb by inducing spinal anæsthesia. The skin temperature of the extremity is estimated accurately before, and at intervals afterwards, and the response noted. If the collateral vessels are capable of dilatation, the skin temperature rises abruptly, perhaps to within a few degrees of blood temperature; if they are diseased, the rise is slower and incomplete.

In a typical case, at room temperature 15° C., the skin temperature of the extremity may be about 18° C. If the collateral circulation is healthy, after induction of the anæsthesia the temperature may rise to 80° to 84° C.; if diseased to 25° C. or so.

(Another method, applicable to either upper or lower limbs, is to

abolish vasomotor control by raising the temperature of the blood going to the limb. This may be effected by heating the trunk in a heat cage, or by immersing one of the limbs not being tested in hot water.

ARTERIAL DEGENERATIONS

The nature, incidence and supposed causes of the various forms of arterial degeneration are adequately treated in most text-books of medicine and of general pathology, and here it will only be necessary to describe those aspects of surgical interest.

It may be recalled that the various degenerations are of common occurrence in the male sex after the age of fifty or sixty years, and that when they occur at an earlier age they are generally associated with some specific cause such as syphilis, diabetes, nephritis, alcoholism or plumbism. Furthermore, it may be mentioned that at least three fairly distinct types of degeneration are recognized. (1) *Atheroma*, a patchy disease principally affecting the aorta, the coronary and cerebral vessels, and characterized by fatty and fibrous changes in the deeper parts of the intima, with loss of elasticity and finally softening and the formation of "ulcerated" plaques. (2) *Arteriosclerosis*, a widespread affection characterized by more or less generalized increase of the fibrous tissue elements of the arterial wall. (3) *Annular calcification* (Mönckeberg's sclerosis), characterized by fibrosis and calcification of the middle coat of medium-sized and smaller vessels.

The various forms of arterial degeneration are of especial interest for the surgeon, for by narrowing the peripheral vessels and interfering with their elasticity these

diseases cause (progressive impairment of the blood supply, and ultimately may lead to gangrene.) In subjects otherwise healthy the circulation may become much diminished, yet suffice to maintain the vitality of the part, and consequently gangrene rarely supervenes before the age of sixty-five or seventy years (senile gangrene). In subjects affected by diabetes, on the other hand, the presence of the poisonous products of faulty metabolism greatly reduces the vitality of the tissues and lessens their resistance to infection, and consequently gangrene occurs at a somewhat earlier age (diabetic gangrene).)

Senile Gangrene. This condition affects males far more frequently than females, and it is uncommon before the age of sixty-five years. The gangrene is generally preceded by premonitory indications of the failing vascularity of the part, such as numbness, tingling, cold, and

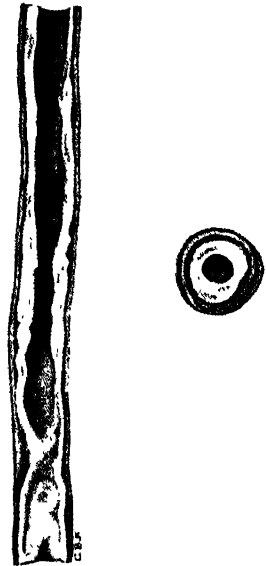


FIG. 110. Diabetic endarteritis of the femoral artery.

(By courtesy of Prof. J. W. S. Blacklock.)

severe cramp-like pains. The great toe is most commonly the part first affected, especially on the dorsum, close to the nail. Often the onset of the gangrene is determined by slight trauma or by mild infection, such as may follow the removal of a corn.

The skin of the toe at first is dead white; later it becomes discoloured by altered blood pigment, and, finally, it becomes black, shrunk and mummified. Since the reduction of vascularity occurs slowly, there is no flooding of the part with venous blood and no sudden stagnation of fluid in the tissues. Consequently the part usually remains dry—at least, near the skin surface—and little, if at all, infected.

The disease progresses very slowly and, indeed, may remain with little change for a period of months. Later the other toes may be involved, and eventually the remainder of the foot. At any time the access of infection may lead to great increase in the rapidity of spread. If the blood supply to the zone bordering on the gangrenous part be adequate an inflammatory reaction may occur, and ultimately result in a line of demarcation. After a very long period the gangrenous part may be shed, and since the blood supply to the muscles and bones is more liberal than to the skin, the resulting stump is conical.

Diabetic Gangrene. This condition is more properly termed “arteriosclerotic gangrene occurring in diabetic subjects,” for it is due primarily to sclerotic changes in the vessels, though the progress is accelerated and aggravated by the underlying disease.

Diabetic gangrene is commonest in male subjects, and it is rare before the age of fifty years. Like senile gangrene, it begins almost invariably in the foot, especially in the neighbourhood of one of the toe-nails. The toxic products of faulty fat metabolism, which are responsible for many of the general effects of diabetes, precipitate its onset even before the arteriosclerotic change is far advanced. Moreover, the toxic products impair the resistance of the tissues to infection and diminish the general vitality of the patient, so that rapid extension to the foot complicated by infection is usual.

Embolic Gangrene. This form of gangrene is not common, but it is of particular importance because a timely removal of the obstructing embolus from the affected vessel may restore the circulation. Migrating emboli usually take the form of a partly organized clot which has developed usually in the left auricle as a result of circulatory stasis in the course of a decompensated heart lesion; less often it arises from the surfaces of an atheromatous ulcer in the aorta. It has occurred as a rare post-operative complication in stout subjects. It is the large arterial trunks, such as the bifurcation of the aorta, the iliac, the femoral and brachial arteries, which entrap the embolus. The femoral artery is by far the commonest site (54%). The embolus is arrested where an artery narrows, its point of bifurcation, and usually it straddles it. Arrest of the circulation leads at once to severe pain from ischæmia, pallor followed by lividity, and, after a variable interval, gangrene at a level depending on the site of vascular occlusion. The advent of gangrene is the outcome not of the local vascular obstruction but of vascular spasm and progressive intravascular clotting extending distally from the embolus.

RAYNAUD'S AND ALLIED DISEASES

In 1862 Maurice Raynaud described a number of cases of obscure ætiology, in which the most prominent features were intermittent pallor and cyanosis of the extremities precipitated by cold. It is now recognized that this syndrome, generally described as the *Raynaud phenomenon*, is not attributable to a single disease, but may occur under the following conditions:—

(1) In healthy persons subjected to extreme cold long enough to lower the body temperature by several degrees.

(2) In sufferers from so-called *hereditary cold fingers*, a familial disease affecting either sex and generally originating in childhood.

(3) In workers using vibrating tools, e.g., pneumatic drills and riveters.

(4) In the incipient stages of degenerative vascular diseases, such as thrombo-angitis obliterans, arteriosclerosis, etc., and of sclerodactyly.

(5) Idiopathically.

The term *Raynaud's disease* is best restricted to the idiopathic form. This is a rare affection, which occurs almost exclusively in women, appearing first between the ages of twenty and forty years. It affects the fingers and hands and sometimes, though usually less severely, the feet as well; the nose and ears are not affected. The attacks, which are nearly always symmetrical, are precipitated by exposure to cold (say, 18° C.), but in about half the cases emotional disturbance may be responsible. The colour change in the skin is a dusky blueness, starting in the finger tips and associated with numbness and pain, followed usually by a waxy pallor if the stimulus persists: warming of the part terminates the attack and the skin assumes a lobster red colour, which gradually fades. No bleeding follows a prick of the finger during an attack. Between attacks the skin is usually normal. Without treatment the condition may progress and culminate in superficial ulcerations or even gangrene of the skin, especially of the little and ring fingers.

The ætiological factors are not yet understood. That emotional disturbance may precipitate attacks suggests that an endocrine or centrally originating vasomotor influence may be responsible for the peripheral vaso-constriction, but against this supposition is the observation that regional "nerve block" will not abort an attack in progress and that sympathetic denervation does not entirely abolish their repetition. Lewis's detailed studies afford strong evidence that the colour changes are due to obstruction in medium-sized arteries, due to an unexplained fault in their vasomotor tone—an unusual susceptibility of the vessel walls to cold.

Acrocyanosis resembles Raynaud's disease except that the blanching phenomena are absent. During the attacks, which follow exposure to cold, there is usually diminished sensibility or even anæsthesia within the affected area of skin. Pain is absent during the attack, but it may be severe and burning in character as it passes. The hand assumes a

vermillion red colour at the termination of an attack. Trophic ulceration of the skin may occur in progressive cases.

Erythrocyanosis frigida (known also as Bazin's disease), affects young women whose legs are unusually fat and thick. In winter the skin of the lower part of the backs of the calves and the ankle region becomes the seat of dusky reddish-purple indurated patches. The malady is bilateral, worse usually on one side than the other; and in severe cases the skin over the discoloured patches breaks down, leaving indolent shallow ulcers.

Part of the swelling of the legs is due to overgrowth of subcutaneous fat and areolar tissue. It may be particularly excessive in the form of pads about the lateral malleolus. The presence of giant-cell formations in the tissue removed from the leg ulcers led to the supposition that tuberculosis might be an underlying cause. More likely the giant cells are of the foreign body type associated with the necrotic process.

THROMBO-ANGEITIS OBLITERANS

This disease was first described, under the title *endarteritis obliterans*, by v. Winiwarter in 1879, but it has only received widespread recognition since Buerger in 1908 drew attention to its characteristic features and gave it the name it now bears.

Thrombo-angietis obliterans is a disease of arteries and veins. In the great majority of cases it affects the vessels of the lower limb, but sometimes it involves the vessels of the forearm, and, exceptionally, the testicular artery and other vessels. It is characterized by low-grade inflammatory changes in the vessel walls with thrombosis in the lumen and much fibrosis in the perivascular tissues, and it takes a progressive course which may culminate in gangrene of the affected extremity. The vessels of the other lower limb may be involved subsequently, sometimes after the lapse of several years.

Unlike most other forms of vascular disease, thrombo-angietis obliterans arises usually before the age of fifty years, and frequently it occurs between the ages of twenty and forty years. Almost invariably it affects males, and for some undetermined reason it is commonest in Jews of Russian origin, though it is not, as was once suggested, limited to that race.

The cause of the disease is unknown. There is no demonstrable relation to syphilis, tuberculosis, arteriosclerosis, or other disease. The pathological changes are those of a low-grade inflammatory process, and it has been presumed that the cause is some form of infection or toxæmia. The valuable therapeutic result achieved in early cases by sympathectomy suggests that arteriospasm of nervous origin may be a factor in its causation. It is well recognized that such spasm if long-continued may lead to marked organic changes in the vessel wall.

In the affected region the most striking pathological change is perivascular fibrosis, and this may be so extensive as to bind the artery with its vein and any accompanying nerves in a dense cord of cicatricial tissue, from which they can only be dissected with difficulty. The

artery when cut across is seen to be contracted, the wall greatly thickened, and the lumen narrowed or quite obliterated.

Microscopically, there is an infiltration of all the coats of the vessels by lymphocytes and plasma cells. The intima is somewhat thickened by proliferation of its endothelial cells, and the muscle fibres of the media are atrophied, but the greatest change is seen in the adventitia, which is extensively infiltrated by fibrous tissue. The internal elastic lamina is not destroyed as in atheroma, but is thickened and sometimes duplicated.

The lumen of the vessel is occupied in whole or in part by a thrombus, which in old-standing cases is organized and fibrous. Sometimes

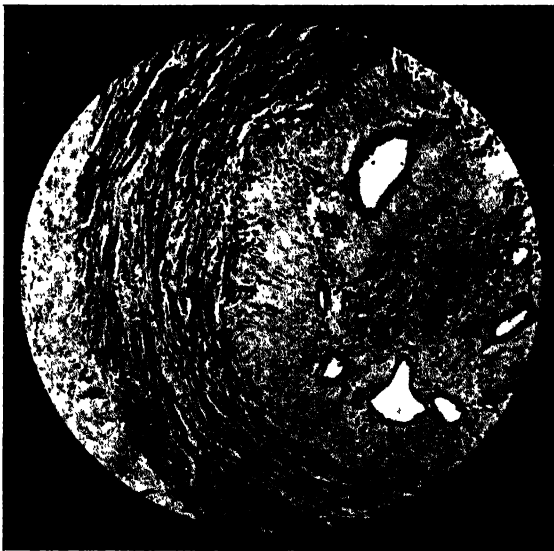


FIG. 111. Thrombo-angitis obliterans. The lumen of the artery is occupied by organized thrombus which has been recanalized.

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the thrombus contains accumulations of round cells with occasional giant cells of the foreign-body type. Canalization of the thrombus occurs as in other forms of intravascular clotting. The new channel may be visible as an irregular, centrally placed lumen, but it is never of large size, and since the fibrosis around prevents dilatation it does not suffice to maintain the nutrition of the part.

Thrombo-angitis obliterans is a slowly progressive disease. Usually it appears first in the main vessels of the foot and leg, especially in the dorsalis pedis artery and in the distal portions of the anterior and posterior tibial arteries. Later it tends to spread proximally and may involve the popliteal artery and even the femoral and iliac vessels. The distribution of the disease is not uniform but patchy, and a vessel

diseased over a length of a few centimetres may be unaffected in the rest of its course.

Since the disease is at first confined principally to the larger blood vessels and is of slow progress, a collateral circulation usually develops sufficiently to maintain, though imperfectly, the nutrition of the limb, but eventually as the obliterative process extends and especially when the popliteal artery is occluded, the collateral circulation proves inadequate and gangrene results. The gangrene is usually of the dry type, and remains confined for long to one or more of the toes.

Gangrene, although the final result, is by no means the most distressing one. For a long time before this stage is reached, impoverishment of the blood supply and involvement of nerves in the perivascular fibrosis give rise to recurrent or continuous pain. Ischæmia of the muscles causes paroxysmal cramp-like pains after even gentle exercise. Impaired nutrition of the tissues, and involvement of autonomic nerves, lead to coldness, blueness or œdema of the extremity and to painful superficial ulcers about the toenails. Phlebitis of superficial veins adds to the discomfort. Eventually pain may be so great as in itself to justify amputation.

VARICOSE VEINS

Dilated and varicose veins occur most frequently in the lower limbs, in the anal canal (hæmorrhoids), and in the spermatic cord (varicocele), but in various conditions of disease they may occur in many other parts of the body. In the three situations just mentioned the varicosities depend upon several related factors, which will be considered in more detail below. In other situations varicosity is almost invariably the result of obstruction to the normal venous flow—for example, the varicosities at the lower end of the œsophagus and elsewhere in cirrhosis of the liver, those of the superficial abdominal veins in thrombosis of the inferior vena cava, and those of the superficial thoracic and cervical veins in obstruction of the superior vena cava. One exception to this general statement is the varicosity which follows the establishment of an arterio-venous aneurysm, in which the dilatation of the vein is due to the intensified pressure from the inflow of arterial blood (*see* p. 231).

Varicose Veins in the Lower Limb

Varicose veins in the lower limb affect adults at any age, and they are especially common between the ages of twenty and forty years. The varicosity may affect any of the superficial veins of the lower limb, and not uncommonly the condition is bilateral. The main trunk and principal tributaries of the great saphenous are the veins most frequently affected. Sometimes only a short segment of a single vein is noticeably dilated, but more often the dilatation is widespread and may affect every subcutaneous vein in the limb to a greater or less extent. In some subjects, especially stout elderly females, innumerable cutaneous venules participate in the dilatation.

From the ætiological standpoint two distinct types of varicose veins may be recognized. Of these the second type is the commoner and the more important.

(1) In the first type the cause is some organic obstruction to the venous return flow, such as may result from the pressure of an intra-abdominal tumour or fluid collection or from extensive thrombosis in the main venous trunks. Post-operative thrombosis (*phlegmasia alba dolens*) and thrombophlebitis complicating such infections as pneumonia and typhoid fever, are examples of such organic obstruction, and they notoriously give rise to very extreme forms of varicosity. It seems probable that the varicosities that occur so often during pregnancy belong to this class and result from pressure of the enlarged uterus on the pelvic veins. The special practical importance of this type lies in the necessity for recognizing the futility of local treatment unless, or until, the primary cause be overcome.

(2) In the second, the more common type, no organic obstruction is present. This is the form so common in young adults. It affects males more often than females, and a familial incidence may be discernible. From the ætiological standpoint this type is of especial interest, for it is apt to occur in two totally distinct classes of subject, namely, in hyposthenic subjects of sedentary occupation, and in athletes.

The cause of varicose veins of this type is generally assumed to be related to some congenital weakness in the vessel wall or supporting tissues, which may be accompanied by, or lead to, a deficiency of the valves. The valvular incompetence thus produced subjects the veins to an increased pressure from within, and, in the upright position, to the weight of an extended column of blood reaching as far as the heart. In addition to such hypothetical developmental weakness, however, there are probably other causative factors, which are related to the general structure and efficiency of the venous system.

In this connexion Wood Jones has drawn attention to several features in the anatomy of the venous pathway which deserve more general recognition. Venous blood, unlike arterial blood, has no *vis a tergo* from the heart beat, nor have the veins more than slight intrinsic pulsatile contractibility, and consequently, in the lower limbs, where gravity increases the difficulty of the venous return, the blood flow depends principally upon the contractions of the skeletal muscles.

Now, in so far as the deeply situated veins are concerned the anatomical disposition is such as to assist this propelling action on the part of the muscles. The deep veins of the leg form multiple channels, irregular and variable *venæ comites*, buried deep in the muscle masses and necessarily compressed by every muscular contraction. At the flexure of the joint these several channels converge upon a single large vessel, the popliteal vein, and this vein is furnished with two or three bicuspid valves, which effectually prevent regurgitation of blood when the muscles relax. A somewhat similar disposition obtains in the thigh.

The superficial veins, on the other hand, lie unsupported in loose subcutaneous tissue, and in normal circumstances are merely subsidiary. Between the superficial and deep systems, however, are several com-

municating channels, notably at the saphenous opening and at the popliteal space, and in conditions in which the pressure in the deep veins is raised these communicating channels transmit the excess blood to the superficial system, which thus becomes a temporary receptacle for the excess blood.

In sedentary persons gravitation effects a passive venous congestion of the whole limb. The deep veins being surrounded by muscles are well supported, and transmit the increased pressure to the superficial veins, and these, being unsupported, dilate. In athletes, on the other hand, there is an *active* venous congestion, following the increased vascularity of the contracting muscles. Moreover, in athletes the muscle contractions, being sustained rather than intermittent, have no pump-like action, but, on the contrary, tend to obstruct the deeply placed veins, and thus the blood is diverted superficially.

The *effects* of varicose veins (of whatever cause) are characteristic. The veins dilate, increase in length and become tortuous and often sacculated. The vessel wall becomes thickened by fibrosis and its muscle fibres atrophy, with the result that the vessel when cut or ruptured gapes widely, permitting free and sometimes fatal hæmorrhage. Adjacent portions of a tortuous vein may become bound together by fibrous tissue and are often closely adherent to the skin, which itself ultimately undergoes atrophic changes.

Stasis of blood in the veins and congestion in the perivascular tissues lead to the deposition of hæmosiderin, and when the veins lie close to the surface, as on the medial surface of the leg, the skin may become deeply pigmented.

Irritation by the pigment, combined with diminished vitality of the tissues from congestion, and often assisted by the effects of dirt and infection, may lead to dermatitis in this region, and later to the formation of an ulcer, which is slow to heal and very apt to recur.

In addition, varicose veins are very liable to thrombosis and phlebitis, which may follow injury or may arise in the absence of any demonstrable cause. Thrombosis may subsequently lead to the formation of small calcified nodules (phleboliths) in the obliterating thrombus.

Hæmorrhoids

Internal hæmorrhoids result from dilatation and varicosity of the superficial veins of the anal canal. These vessels, which are anastomosing channels between tributaries of the superior and inferior hæmorrhoidal veins, lie in the submucous tissue superficial to the sphincter muscles, and being ill-supported they readily dilate.

In the great majority of cases the essential factor in the production of hæmorrhoids is chronic constipation. The presence of large scybalous masses in the rectum induces a degree of venous stasis, and this is greatly aggravated by prolonged straining at stool. It seems probable that in some subjects there is a weakness of the vessel walls, which predisposes to the dilatation. Occasionally hæmorrhoids arise as a result of obstruction to the portal blood flow, for example, in cirrhosis of the liver. Hæmorrhoids are of common occurrence in pregnancy, from pressure

of the enlarging uterus upon the superior hæmorrhoidal vein. It is important to recognize also that they may result from the pressure of a tumour within the rectum, and may provide the first indication of such disease.

Fully developed hæmorrhoids form dark purplish polypoidal masses which project into the anal canal. Most commonly three large hæmorrhoidal masses are present, one situated anteriorly and the other two on the posterolateral aspects of the canal, and in addition there are usually several smaller masses. The masses tend to protrude at the anus, usually only during prolonged straining at stool, but sometimes upon the slightest exertion. Even when small they may bleed freely and may even give rise to a severe degree of secondary anæmia. Infection may occur, especially if the masses remain protruded at the anus. Infection commonly leads to thrombosis within the hæmorrhoidal vein and sometimes to ulceration or necrosis of the pile. Rarely such infection has been known to lead to pyelephlebitis.

External hæmorrhoids result from dilatation and varicosity of anastomosing veins situated deep to the peri-anal skin. Commonly they give rise to small firm piles or skin tags. Occasionally the vein ruptures as a result of sudden straining at stool and the extravasated blood clots, forming an exceedingly painful "thrombosed pile."

Varicocele

This is a varicose condition of the veins of the pampiniform plexus. It occurs in young men, and is almost always confined to the left side. Little is known of the ætiology, but it seems probable that, as in the case of varicose veins of the lower limbs, there is a developmental weakness of the vessel walls. The affected veins become dilated and extremely tortuous, and from the weight of the contained blood they may cause a certain amount of discomfort.

Varicocele may occur in older men, and is then usually due to pressure of a tumour upon the testicular vein or, on the left side, on the renal veins. A hypernephroma of the left kidney growing along the lumen of the left renal veins has been known to have this effect.

TRAUMATIC ASPHYXIA—Traumatic Cyanosis

This rather rare condition results from (severe, but briefly sustained, crushing injuries to the thorax, such as may occur in railway or pit accidents, or, rarely, from the pressure in densely packed crowds.) It is characterized by a (generalized purple suffusion and œdema of the skin of the face and neck and diffuse ecchymosis of the conjunctiva.) It may be accompanied by fracture of the sternum or ribs; and from injury to the minute vessels in the retina it may lead to temporary or permanent blindness.

The (distribution of the very striking discoloration is sharply demarcated.) In front it extends to a short distance below the clavicles; posteriorly its inferior limit is variable, but it usually reaches the level of the upper part of the shoulder girdle.

The condition is due to sudden distension of the veins of the upper part of the head and neck as a result of sudden occlusion of the large veins at the thoracic inlet, and the peculiar character and the wide extent of the lesions are attributed to the absence of valves in the cervical veins.

The discoloration of the skin is due to dilatation of veins and capillaries, associated probably with temporary loss of their elasticity. Hæmorrhage of any considerable size is very unusual. The œdema and suffusion recede gradually, and with less change of colour than is observed when an ecchymosis fades. Before absorption is complete the skin may have a blotchy yellow-green colour which is slow to disappear.

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CHAPTER XII

DISEASES OF LYMPH GLANDS AND VESSELS

By reason of their intimate relationship to the tissue spaces the lymph channels form an easy route for the spread of bacterial infections and for invasion by malignant cells. Consequently the lymph vascular system is of primary importance to the surgeon in relation to acute and chronic infections and to malignant neoplasms.

The radicles of the lymph system originate in minute intercellular culs-de-sac, and by union they form larger vessels which terminate in the lymph glands. Efferent vessels from the glands eventually empty their contents into the venous blood stream, either by the thoracic duct or by other main lymph channels. A typical lymph gland is somewhat kidney shaped, and it consists of a fibrous capsule, from whose deep surface spring fibrous trabeculæ, and a parenchyma of lymphoid tissue. A more or less distinct hilum may be recognized, which admits the artery to the gland and forms the point of exit for the veins and the efferent lymph vessel.

The afferent lymph vessels, usually multiple, enter the gland at its convex surface, and, having pierced the capsule, they communicate directly with a subcapsular lymph space known as the "corridor" of the gland. Lymph percolates through the meshes of the corridor and thence to finer channels known as lymph sinuses. In the sinuses the lymph stagnates in close contact with the endothelial cells of the lymph cords, and any particles such as bacteria or pus cells may be arrested there and undergo phagocytosis. From the sinuses the lymph passes towards the hilum of the gland and is collected into the main efferent vessel.

It may be noted that a lymph gland subserves two distinct functions, the one concerned with arrest and destruction of substances in the lymph, the other with the formation of lymphocytes by the germ centres of the follicles. Each of these functions is of great importance in relation to the pathology of the lymph vascular system.

OBSTRUCTION OF LYMPH VESSELS

Obstruction or obliteration of lymph vessels is a common result of acute and chronic inflammatory diseases and of cancer. When the obstruction is localized the collateral channels are usually sufficient to carry on drainage, but when the obstruction is extensive, or involves large lymphatic trunks, stagnation of lymph in the tissues results, and the affected part becomes œdematous, or, in the case of serous cavities, an effusion occurs. In many cases lymphatic obstruction is temporary and its effects disappear when the disease responsible for it subsides; but in other cases, especially those associated with cancer or chronic

infective disease, the obliteration of the lymph vessels is progressive and permanent, and a state of chronic œdema is established. Clinically, lymphatic obstruction is observed most often in the lower extremities, the external organs of generation, and less often in the upper extremity. The obstruction may be due to extensive removal of lymph glands, to infective diseases, such as erysipelas or tuberculosis, or to widespread invasion of the lymph glands and their tributaries by cancer cells. In some instances a combination of factors is present.

The lymph vessels and the veins are functionally very similar, and their intimate association is evidenced by the great increase in lymph flow which occurs in a limb when its main vein is ligated. In the same way, probably, the veins may, in part, compensate for the effects of obstruction of the lymph vessels. In many diseases lymphatic and venous obstruction coexist, and when the obstruction is severe a very marked state of temporary or permanent œdema occurs which may finally give rise to the condition known as *solid œdema*.

Elephantiasis. Elephantiasis is a condition of overgrowth of the skin and subcutaneous tissues in a part subjected to prolonged lymph vascular obstruction; It occurs most often in the lower extremities and the external genital organs, and less often in the upper extremities and in the face. The swelling is due essentially to obstruction of the lymph vessels and glands in various ways, but as it is often preceded by a condition of solid œdema it is generally held that there must also be obstruction of the venous return in the affected part. The obstruction of the veins is usually due to thrombophlebitis caused by secondary infection from the skin or the blood.

The œdematous fluid in which the tissues are bathed is rich in protein and stimulates proliferation of fibrous tissue beneath the skin. On account of the stress from within and stagnation of lymph, the skin becomes coarse, thick, and corrugated, and is often discoloured. Sometimes it bears wart-like projections, or it may exhibit excoriation or ulceration.

Various types of elephantiasis are described according to the diseases which originally determined the lymph vascular obstruction.

Congenital elephantiasis is a rare affection of unknown causation. It is sometimes familial. One lower extremity is usually involved. The swelling is not very great in early life, but it increases during adolescence, and if untreated it eventually becomes enormous.

Filarial elephantiasis is the commonest variety and occurs in tropical countries. It is due to invasion of the lymph vessels and glands by the adult worm of the *filaria sanguinis hominis*. It is believed that the filarial infection is merely a predisposing cause of the lymph-vascular obstruction, and that the exciting cause is lymphangitis, due to superadded septic infection from foci elsewhere.

The disease attacks any part, but the lower extremities and the external genitals are the common sites, and the enormous size which these parts may assume is well known. When incised at operation the skin and subcutaneous tissue are found to be irregularly thickened, due to overgrowth of the fibrous tissue and to the loculation of œdematous fluid. The superficial veins are often dilated.

Lupus elephantiasis, now rare, occurs in young women and usually follows upon lupus of the toes and feet which has extended to the subcutaneous lymph vessels. As the lymph vessels become obliterated the skin and cellular tissues become hypertrophied. The skin is studded with fungating masses or ulcers of a livid blue colour. There is usually a concomitant infection by pyogenic organisms which may lead to gangrene.

Elephantiasis græcorum is due to infection of the skin and subcutaneous tissues with the lepra bacillus. The disease chiefly attacks the face, which becomes the seat of tumour-like masses consisting of leprous nodules.

Elephantiasis due to cancer is seen in its most characteristic form in the upper extremity as a result of obstruction of the axillary lymph glands and the axillary vein in carcinoma of the breast. Sometimes it follows operation. The whole limb is enormously swollen and may be the site of multiple ulcers. Usually there is considerable pain, or the limb may be rendered useless.

Elephantiasis neuromatosa is a condition sometimes associated with neurofibromatosis. It is described on p. 321.

ACUTE LYMPHADENITIS

Acute inflammatory enlargement of a lymph gland may result from any infective process in its catchment area. It is especially apt to follow interstitial infections with pyogenic organisms, particularly streptococci, and is less common in catarrhal conditions. The lymph glands affected most frequently are those of the antecubital fossa and the axilla in infections of the hands, those of the neck in infections of the scalp, face, tonsil or pharynx, and those of the inguinal region in infections of the genitalia and the anal region.

The earliest result of infection of a gland is proliferation of the endothelial cells lining the lymph sinuses, and these cells by their phagocytic action are able to deal with many of the organisms as well as the effete pus cells borne in the lymph from the initial focus. If the infection is more severe, the lymphoid tissue plays merely a passive part, and an inflammatory reaction similar to that seen in other tissues occurs. The blood stream is slowed, fibrinous fluid exudes, and polymorph leucocytes escape into the meshes of the gland. At this time the gland is enlarged, congested, and very tender. If the infection is overcome, the inflammation may resolve completely, but if the infection continues, suppuration results. The abscess thus formed may remain limited to the gland, and may subsequently undergo partial absorption, fibrosis and calcification, but much more often it spreads beyond the confines of the gland, extends widely in the tissue spaces, and gives rise to serious local and constitutional effects.

CHRONIC NON-SPECIFIC LYMPHADENITIS

Chronic non-specific lymphadenitis is a comparatively uncommon condition, for the reaction of lymph glands to infection is so vigorous

that any inflammation short of suppuration subsides as soon as the primary focus of infection is overcome. Consequently chronic lymphadenitis is due almost invariably to the persistence of the primary focus of infection. Such chronic primary foci occur most commonly in the gums, the teeth, the tonsils and the scalp, and consequently the glands the seat of chronic lymphadenitis are those of the neck.

TUBERCULOSIS OF LYMPH GLANDS

The important part played by the lymph vascular system in the early spread of tuberculosis has already been discussed (Chapter IV.), and it only remains to consider the special pathological features of the disease in lymph glands.

Tubercle bacilli usually gain entrance to the body in the pharynx,

the lungs, or the small intestine, and consequently the glands first affected are generally those of the neck, mediastinum or mesentery. Tuberculosis of lymph glands usually pursues a chronic course, and often remains limited during a long period to a single gland or a group of glands.



FIG. 112. Tuberculosis of lymph glands. Numerous lymph glands occupied by caseous material are matted together in a solid mass.

(Department of Clinical Surgery, University of Edinburgh.)

Other glands may be infected by way of the lymph or, rarely, by the blood stream, and the localization and character of the lesions differ according to the method of spread. Lymph-borne infection progresses slowly and at first attacks the glands that are close to the primary focus, whereas a blood-borne infection is just as apt to attack distant as local glands. On account of the anatomical distribution of the afferent lymph vessels

the early lesions in lymph-borne infection are situated in the subcapsular region of the gland in close relation to the subcapsular lymph sinus, whereas in blood-borne infection, since the blood vessel to a gland breaks up immediately on entering the hilum, the early lesions are scattered diffusely through the gland.

The pathological changes in a tuberculous gland may take either of two forms, (a) the caseating, or (b) the proliferative. Of these the former is by far the more common.

(a) In the caseating form the changes are those typical of tuberculosis in most other situations. Tuberculous follicles develop, with a central area of endothelioid cells and giant cells and a surrounding zone of lymphocytes. Caseation occurs in the central area, and enlargement of the caseous region and confluence of adjacent tubercles may proceed until the whole gland is replaced by yellow cheesy material. At any stage in the process the disease may be overcome, and then the follicles become replaced by fibrous tissue and ultimately become calcified. Such calcified tuberculous glands are extremely common, especially in the mediastinum or the mesentery of the small intestine, and less often in the neck.

If, on the other hand, the disease progresses, the periglandular connective tissues are involved, and adjacent glands become adherent to one another. Cold abscesses may develop and may infiltrate fascial planes and muscles. Eventually they reach the skin surface and rupture, leaving a tortuous sinus which remains as long as the glandular infection persists.

(b) In the proliferative form the pathological changes are of a different type. Giant-cell systems are scanty or absent, and there is little or no caseation. The glands are swollen and elastic to the touch, and on section they are of fleshy appearance and greyish-pink colour. Microscopically, the characteristic change is a diffuse proliferation of endothelial cells, with a variable degree of fibrosis. It will be obvious that glands affected in this way bear a certain resemblance to the glands of lymphadenoma (*see* p. 258), and not infrequently distinction is difficult.

Tuberculosis of Glands in the Neck. This condition presents certain characteristic features, and in view of its surgical importance merits separate consideration.

Two distinct types of infection may be recognized. In the first, the adenitis is a manifestation of widespread tuberculosis. The patient is thin, pale and anæmic, and active disease is present in the tracheo-bronchial lymph glands, and often in the lungs. The affected cervical glands are multiple and are situated in both sides of the neck mainly in the lower parts of the anterior and posterior triangles. The glands are not greatly enlarged, and are of soft consistency, rarely caseous.

The second type, seen more often in surgical practice, is a purely local infection. The patient, usually a child, is often of healthy appearance, and without evidence of other tuberculous lesions. Generally, one gland is grossly diseased, whilst a few glands adjacent to it are involved to a smaller extent. In most cases the principally affected gland is the jugulo-digastric or tonsillar gland, situated in the angle between the common facial and internal jugular veins. Less often, a gland in the submaxillary region, or in the posterior triangle or the lower part of the neck, is the chief site of the disease.

It seems probable that in this local type of disease the infection gains access to the gland directly from the pharynx, and in the majority of cases the site of entry is at the tonsil. The infecting organism is often of bovine type, and in many cases, no doubt, is milk-borne. Frequently a predisposing factor may be found in a recent

attack of acute tonsillitis or one of the infectious fevers of childhood, particularly measles, whooping cough or scarlet fever.

In this local type of disease the gland principally involved often progresses to caseation and to the formation of a cold abscess. From the tonsillar gland the abscess tracks forwards and downwards to reach the anterior border of the sternomastoid muscle. At this point it perforates the deep fascia, and leads to the formation of a cold abscess under the skin. Not infrequently, the skin over the abscess becomes thinned and breaks down, giving rise to a sinus.

Cold abscess formation may signify complete destruction of the offending gland, but caseous or calcareous fragments may be responsible for persistence of infection and require removal surgically.

TUMOURS OF LYMPH VESSELS : LYMPHANGIOMA

A lymphangioma is similar to a hæmangioma except that its spaces and channels contain lymph. The tumour, which is often of congenital origin, results either from new formation of lymph spaces or vessels, or from dilatation of those which already exist. Usually the tumour is completely isolated from the normal lymph channels, but in some cases communications are present. There are three chief varieties : capillary, cavernous, and cystic.

A capillary lymphangioma occurs most often in the lips, cheeks or tongue or in the skin and subcutaneous tissues, and less often in muscles and internal organs. It gives rise to a localized nodular tumour, or causes diffuse enlargement of the part in which it is situated. For example, in the tongue it leads to one form of macroglossia. On section the tumour is composed of anastomosing channels or spaces lined by flat or cubical epithelium and filled with clear fluid containing a few lymphocytes. The stroma is composed of fibrous tissue. In a few instances, a hæmangioma and lymphangioma are combined.

A cavernous lymphangioma occurs chiefly in the skin, but sometimes in the intermuscular septa or in the mucous membranes, where it may give rise to a circumscribed or diffuse tumour. It is composed of dilated lymph spaces which intercommunicate. The spaces are lined by flat endothelium and contain thin fluid or coagulated lymph. Hæmorrhage may occur in the tumour and thus create the appearance of a hæmangioma.

A cystic lymphangioma occurs chiefly in the neck, axilla and groin, occasionally in the sacral region or great omentum. Less frequent situations are the floor of the mouth, the liver and the suprarenal glands. The cyst is usually thin walled and multilocular and may reach a very large size. It may be present at birth or may appear soon afterwards.

In the neck the tumour is known as a *cystic hygroma*. It may be definitely circumscribed, but frequently it forms a ramifying mass which extends deeply between the muscles, and may even extend to the thorax or axilla. It may disappear spontaneously, but more often this is accelerated by infection of its contents.

LYMPHOSARCOMA

A lymphosarcoma or reticulum-cell sarcoma is a tumour of lymphoid tissue, and is believed to arise from the progenitors of the cells of lymphoid tissue. It is characterized by rapid growth and a high degree of local malignancy. It occurs most commonly in young subjects and it progresses rapidly to a fatal issue.

The tumour may originate in a lymph gland or in any other collection of lymphoid tissue. Most frequently it arises in one of the glands of the neck or the mediastinum, or in the tonsil or the lymphoid tissues of the nasopharynx. In other cases it may arise in the mesenteric or retroperitoneal glands or in the lymphoid tissue of the gastrointestinal tract. Rarely it occurs in any tissue in which lymphoid tissue is present.

The tumour grows rapidly and attains large size. It is usually of pale colour and soft consistence, and is very liable to necrotic softening and hæmorrhage. It spreads from the site of origin, infiltrating surrounding tissues and involving other lymph glands in the vicinity. Subsequently more distant glands are affected, apparently by extension along lymph vessels, and ultimately small metastases may develop in the liver, spleen or other organs. Microscopically, the normal architecture of lymphoid tissue is lost, and the tumour consists almost entirely of small, round, dark-staining cells, supported by very scanty stroma. Sometimes larger cells of endothelial type are present, which are regarded variously as primitive lymphoblasts or as endothelial cells derived from the lymph cords.

In some cases the reticulum cells of the lymph sinuses are represented, and deeply staining argyrophil reticulum fibrils are a prominent feature (*reticulum-cell sarcoma*).

Lymphosarcoma in the neck forms a bulky soft mass which becomes fixed to surrounding structures and may ulcerate at the skin. It originates usually in a gland of

the upper deep cervical group or in the tonsil, and spreads thence to involve the glands of the other side and those of the mediastinum or

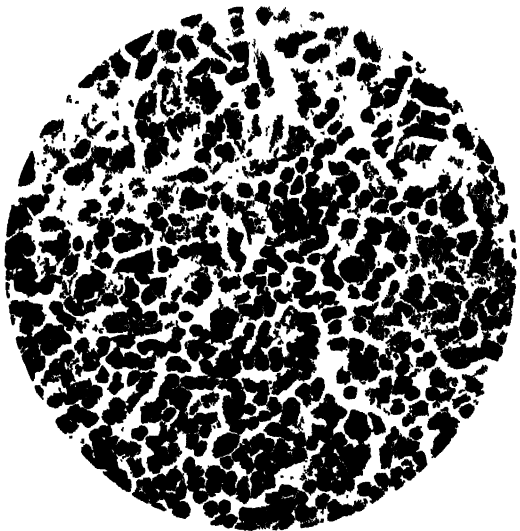


FIG. 118. Lymphosarcoma. The tumour is composed of small round cells with hyperchromatic nuclei, and of larger cells of endothelial type. A few malignant giant cells are present.

(Laboratory of Royal College of Physicians of Edinburgh.)

the axillæ. Lymphosarcoma in the mediastinum tends to spread diffusely in the mediastinal tissue-planes and to invade the lung, and it may give rise to a fatal issue from pressure upon the trachea or great vessels. It may be remarked at this point that mediastinal lymphosarcoma is probably not so common as was supposed at one time, for many of these mediastinal growths are now known to be atypical carcinomata derived from the bronchi, and others are tumours of the thymus.

Lymphosarcoma in the abdomen may arise either in a lymph gland or in the lymphoid tissue of the gastro-intestinal tract. A growth arising in the latter situation occurs most often in the wall of the distal part of the ileum, less often in the jejunum, stomach or colon. It arises usually in the submucous layer and infiltrates the gut wall diffusely, thickening it over a large area and ulcerating at the mucous surface. Sometimes multiple nodules, apparently independent, arise in different parts of the intestine.

LYMPHADENOMA (HODGKIN'S DISEASE)

Lymphadenoma or Hodgkin's disease is an affection of the lymphoid and reticulo-endothelial tissues. It is characterized by painless enlargement of the lymph glands and spleen and by anæmia of secondary type. In some cases the lymphoid or reticulo-endothelial tissues of the liver, lung, bone marrow and alimentary tract are also involved. Generally it affects young adults, especially of the male sex, and it usually progresses during a few years and terminates fatally.

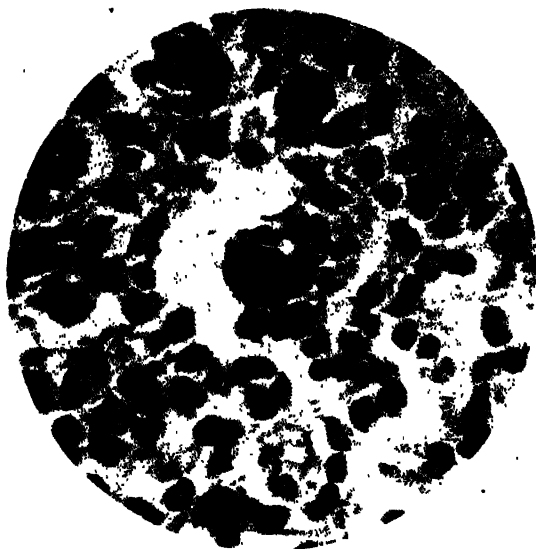


FIG. 114. Lymphadenoma (Hodgkin's disease):
× 900. Note the endothelial cells and the characteristic giant cells.

(Laboratory of Royal College of Physicians of Edinburgh.)

The Lymph Glands. The glandular enlargement is a constant, and generally the earliest sign of the disease. The enlargement is limited at first to the lymph glands in a single region, and it may remain so limited during many months or even years, but later it affects other groups of glands and eventually may affect lymphoid tissues in all parts of the body. The first glands to become enlarged are usually those at the root of the

neck on one or on both sides. In others the glands in the upper part of the neck or in the mediastinum are affected first. Less commonly, the earliest site of the disease is in the glands of the axilla, groin, or retro-peritoneal region.

The affected glands attain considerable size, and when situated within the thorax or the abdomen may give rise to pressure effects. Glands in the mediastinum may exert pressure on the large veins and give rise to venous engorgement and oedema of the face and neck, or they may press upon the trachea and embarrass respiration. Glands in the abdomen may cause obstruction of the alimentary tract or of the portal vein or, rarely, the common bile duct.

On cross section the lymph glands have a characteristic appearance. They are of a uniform, homogeneous character, pinkish-grey in colour, and elastic to the touch. At first they are of somewhat soft, fleshy consistency; later, they are firm and fibrous. The glands do not caseate and never undergo calcification. There is no peri-adenitis, and consequently the glands remain discrete and non-adherent to surrounding tissues.

Microscopically, the appearance varies at different stages of the disease. At first there is proliferation of all the specific cells that take part in the formation of a lymph gland, the reticulo-endothelial cells of the gland "corridor," the endothelial cells of the germ centres, and the lymphocytes which occupy the bulk of the gland. Many of the cells assume immature type, and large lymphocytes and eosinophil leucocytes make their appearance. At this stage giant cells of special type are usually present. Some of them are mononuclear cells, somewhat resembling endothelial cells, from which they probably take origin. Others are multinucleated cells which bear a striking resemblance to the megakaryocytes of the bone marrow.

In the late stages of the disease the microscopic appearance is altered by the growth of fibrous tissue, which infiltrates the whole gland and replaces the cellular elements.

The other Lesions. Whilst enlargement of the lymph glands is an invariable feature of Hodgkin's disease, involvement of other organs is less constant.

The spleen is affected in most cases at some stage of the disease. It is enlarged, sometimes considerably so. In some cases it is uniform and homogeneous in appearance, in others it is nodular, and the cut surface shows the presence of pale rounded masses somewhat resembling suet. Microscopically, the changes are similar to those seen in the lymph glands.

The blood shows the changes characteristic of a secondary *anæmia*. In some cases there is a moderate leucocytosis and there may be an increase in the number of eosinophil cells.

The liver is involved in some cases, and presents a diffuse cellular infiltration along the portal tracts. Rarely the bone marrow, the lungs and the submucous tissues of the stomach and small intestine show a diffuse cellular infiltration or even nodular swellings. Such nodules in the stomach or intestine may project into the lumen and may be mistaken for sarcoma.

The cause of lymphadenoma is not known. The disease has been regarded by many workers as a form of tuberculosis, due to attenuated human or bovine bacilli. While it is true that in a small proportion of cases guinea-pig inoculation of extracts from the affected glands yields a positive result, this may be due to a coincident tuberculous infection, and the negative results obtained in the great majority of cases must be regarded as conclusive evidence against this theory. The view that infection with the avian type of tubercle bacillus is responsible has also now been generally discarded.

In some respects lymphadenoma is comparable to the leukæmias and to lymphosarcoma, and many observers regard it as a type of tumour formation allied to these conditions.

Lastly, there is the view that lymphadenoma is due to infection by organisms of low virulence. The attacks of pyrexia (Pel-Ebstein waves) that form such a characteristic feature of the clinical course give some support to this theory. Various workers have isolated streptococci, diphtheroid bacilli, and other organisms from the affected glands, but their very multiplicity precludes conviction.

SARCOIDOSIS (OF BOECK)

Lymphogranulomatosis Benigna

This rare disease has acquired considerable interest and importance on account of its obscure nature and the multiple and varied pathological lesions it may present. It may be latent, but it usually gives rise to a protracted illness which recovers spontaneously.

The pathological features are mainly the result of proliferative changes in the lymphoid tissues, like those in tuberculosis but without caseation. The lesions are most constant in the lymph glands, but the lymphoid tissue in the lungs, in the salivary glands and other sites may be affected. Skin lesions, in the form of small papules on the face and limbs, are present in half the cases. Bone changes are present in a small proportion.

The lymph gland enlargement is never more than slight and is always painless. One or several groups of glands may be affected: the glands are discrete and freely movable and histologically show segregations of epithelioid cells and scanty giant cells. The bone changes are commonest in the hands and feet, and consist of well-demarcated deposits of sarcoid tissue in the marrow of the phalanges.

The changes in the lungs may resemble peribronchial tuberculous infiltrations or miliary tuberculosis.

Uveoparotitis and possibly Mikulicz's syndrome (chronic swelling of the parotid and lachrymal glands) are believed to be manifestations of sarcoidosis.

The nature of sarcoidosis remains unsolved. It resembles tuberculosis, and some of the cases ultimately succumb to that infection. However, most cases show a negative Mantoux reaction, and attempts at guinea pig inoculation of biopsy material have not succeeded.

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CHAPTER XIII

DISEASES OF THE SKULL AND BRAIN

THE CEREBROSPINAL FLUID

THE existence of a "third circulation," unsuspected until fifty years ago, is now clearly recognized. Cerebrospinal fluid, produced by the chorioid plexus of the lateral and third ventricles, circulates through the ventricular system and over the surface of the brain, and is absorbed into the blood stream in the venous sinuses of the dura mater.

The Production of Cerebrospinal Fluid. It has long been acknowledged that the chorioid plexuses are responsible for the formation of cerebrospinal fluid, and Dandy's work has put the evidence upon a secure experimental basis. In animals, Dandy showed that dilatation of the ventricles can be produced by artificial obstruction to the pathway of cerebrospinal fluid, either at the interventricular foramen (foramen of Munro) or in the aqueduct between the third and fourth ventricles; but if at the same operation the chorioid plexus be removed, no fluid is secreted and the ventricles remain collapsed. The chorioid plexus must therefore be the source of the fluid.

How the fluid is produced remains doubtful. The fluid has sometimes been regarded as an active secretion, for its composition shows a remarkably selective process. Very few drugs reach the cerebrospinal fluid, and even the pigments of obstructive jaundice, which colour all transudates and many secretions, are usually withheld from it.

The fluid differs from every other bodily secretion, in containing the salts and sugars of the blood but practically no proteins. According to Mestrezat, the fluid is a dialysate, escaping from the blood through the colloidal membrane formed by the cells covering the chorioid plexus. All the contents of the cerebrospinal fluid are derived from the blood plasma, and salts, sugars, urea and diffusible organic substances such as alcohol, ether, or chloroform may pass into the fluid, but colloids are completely excluded. Moreover, the flow of cerebrospinal fluid seems to depend upon physical rather than vital influences, for its pressure is regulated by the arterial blood pressure, and increases when venous stasis is brought about.

The Course of the Cerebrospinal Fluid. From the chorioid plexuses the fluid passes through the ventricular system and escapes through the openings in the roof of the fourth ventricle, the central rounded foramen of Magendie and the two lateral slit-like orifices of Luschka, to reach the subarachnoid space. Here it filters through the large subarachnoid cisterns, the cisterna magna on the dorsal surface and the cisterna pontis and its extensions ventrally. A small quantity of the fluid passes along the membranes of the spinal cord, but the larger portion percolates upwards over the surface of the brain. Finally

it is absorbed into the venous sinuses, especially those over the cerebrum.

Absorption of Cerebrospinal Fluid. Weed and his collaborators have demonstrated clearly that the fluid is absorbed into the blood principally through the *arachnoidal villi*. These are delicate structures, composed of arachnoid mater situated in relation to the venous sinuses of the vault and the anterior and middle fossæ of the skull. They resemble small herniæ of arachnoid membrane, protruding through gaps in the dura mater and projecting into the lumen of a blood sinus. The villi are capped by meningocytes (endothelial cells of the meninges) and enclose channels continuous with the subarachnoid space, so that the cerebrospinal fluid is brought into intimate contact with the blood and is readily absorbed. In later life some of the villi, especially those related to the lacunæ of the superior sagittal sinus, become thickened and calcified—the Pacchionian bodies.

The Subarachnoid Space. This is an extensive lake traversed by innumerable delicate strands of tissue, and it forms the pathway for cerebrospinal fluid coursing over the brain surface. It covers the whole surface of the brain and spinal cord, communicates with the ventricles, and extends along innumerable minute channels deeply into the substance of

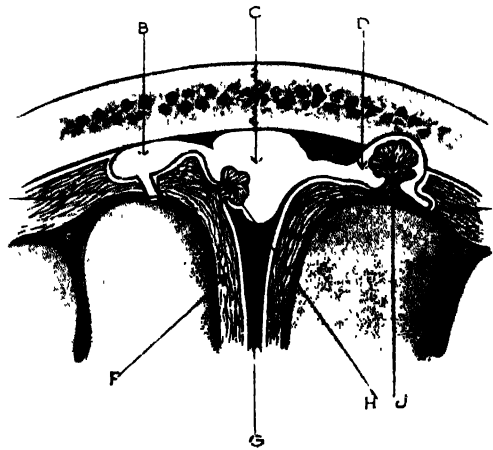


FIG. 115. Site of absorption of cerebrospinal fluid. (A, E, F), subarachnoid space. (B, D), lacunæ laterales. (C), superior longitudinal sinus. (G), falx cerebri. (H, J), arachnoid villi.

(By courtesy of Professor J. Fraser and Mr. N. M. Dott.)

the brain. The space is bounded by two endothelium-lined membranes, the arachnoid superficially and the pia mater on the deep aspect, and it is traversed in every part by a web of delicate interlacing strands connecting the two layers. The outer surface of the arachnoid is smooth and is closely apposed to the deep aspect of the dura mater, and only a potential subdural space exists between the two. The pia mater is firmly attached to the brain, following the contour of its surface into the sulci, and is prolonged deeply as a sheath around all the cerebral vessels. Consequently, in these places the subarachnoid space also extends deeply.

At the base of the brain the pia and arachnoid are widely separated, and here the intervening subarachnoid space expands to form the large basal cisterns. From the deep aspect of the space extensions bounded by pia mater pass into the substance of the brain, investing the cerebral vessels and forming delicate sheaths containing cerebrospinal fluid, which comes into intimate contact with every nerve cell. These peri-

vascular spaces have the function of lymph channels, for there are no true lymph vessels within the brain.

* The fluid-filled cavities of the subarachnoid space are lined by delicate mesothelial cells or meningocytes, which resemble the peritoneum in exhibiting a remarkable capacity for repair. This action is called into play in a most striking way when there is an escape of cerebrospinal fluid beyond its normal confines. If, for instance, in the treatment of hydrocephalus, drainage of cerebrospinal fluid into the loose tissues of the scalp is established, a rapid proliferation of the leptomeninges occurs, and the leak is closed forthwith.

Functions of the Cerebrospinal Fluid. In the jolts and jars of daily life the cerebrospinal fluid probably tends to protect the delicate nerve cells of the brain, insulating them in this way and acting as a sort of water cushion. It is of interest to note that the fluid is most abundant around the part of the brain that it is most important to protect—the medulla. In pathological conditions the fluid is of value as an inert mobile tissue that can be displaced to make room for the cranial contents. Its most important function, however, is that of a vehicle for the excretion of the products of metabolism of nerve tissue, in this respect compensating for the absence of lymph. It probably acts also as the vehicle whereby the internal secretions of the pituitary gland reach the blood stream.

HYDROCEPHALUS

Brief consideration of the physiology of the third circulation suffices to show that hydrocephalus may theoretically result from one of three processes, namely (1) increased secretion of cerebrospinal fluid beyond the limits of normal absorption, (2) obstruction to the flow in any part of its course, or (3) failure in the process of absorption. In practice, examples of the first process are rare, those of the third are uncommon, and the great proportion of cases are due to the second process and are thus examples of *obstructive hydrocephalus*. Obstructive hydrocephalus may occur in adult life, but is most common in infancy.

Hydrocephalus in adult life is usually due to the pressure of a tumour, rarely to obliteration of the ventricular foramina or of the subarachnoid space by adhesions following leptomeningitis. A tumour may obstruct the flow of cerebrospinal fluid directly or indirectly. A tumour of the acoustic nerve may press directly upon the mid-brain and so constrict the aqueduct, or a tumour of the cerebellum may close the pathway at the fourth ventricle. More often, however, a tumour acts indirectly by displacing the brain stem towards the foramen magnum. This forms a "pressure cone" by impaction of the cerebellar tonsils and the medulla in the foramen, and obstructs the outflow of cerebrospinal fluid from the fourth ventricle.

Hydrocephalus in infancy may result from a congenital abnormality or may be due to obstruction to the fluid pathway by sypilitic meningitis or by adhesions following a birth hæmorrhage. The obstruction may occur in the aqueduct of Sylvius, the foramina in the roof of the fourth ventricle may be occluded, or adhesions over the surface of the

brain may bar the progress of the fluid towards its area of absorption. Thus the obstruction may be intraventricular or extraventricular.

In the latter type of case not infrequently a spina bifida co-exists. The spinal defect then acts as a safety valve, absorbing the excess of cerebrospinal fluid. Recognition of this coexistent deformity is of



FIG. 116. Hydrocephalus. The membrane bones of the skull are extremely thin, and the fontanelles are of large size.

(*Museum of Royal College of Surgeons of Edinburgh.*)

importance, for surgical repair of the spinal defect may aggravate the hydrocephalus.

In any type of hydrocephalus the end result is the same. The obstructed ventricles become dilated, compressing the tissues of the brain to a thin shell. The white matter is affected first and in greater degree; the grey matter resists for a much longer period. In childhood incomplete ossification permits the skull to become enlarged and globular, contrasting remarkably with the tiny pinched face. The cranial bones separate widely and in the extreme stages parts of the skull are represented only by a thin stretched-out membrane.

INJURIES TO THE SKULL AND BRAIN

It is a commonplace that in head injuries the damage to the brain is often out of all proportion to the damage to the skull. Injuries which at first sight appear trivial, with no damage to the skull or only a small fissure, may prove fatal from their effect upon the brain or its vessels. Conversely, gross compound depressed fractures may, though uncommonly, be complicated by little evidence of injury to the brain. Fractures of the skull may cause tearing of cranial nerves or may provide a pathway for leakage of cerebrospinal fluid, and thus favour the access of infection, but in other respects their importance is small compared with the associated damage to the brain.

A head injury presents a complex physical problem. The effects are dependent upon the shape and size and speed of the striking force and upon the strength and elasticity and degree of fixity of the cranium. Thus at one extreme a blunt injury may cause prolonged unconsciousness but no permanent damage to the skull or brain, while at the other, a high velocity bullet may penetrate the brain or an airplane propellor may slice off a part of the skull without causing even momentary concussion.

Apart from war wounds, most injuries to the head are "blunt" injuries caused by the impact of a large mass. Such injuries commonly cause concussion and they may give rise to all degrees of bruising or lacerations of the brain and to extensive hæmorrhages, intracerebral, subdural or extradural.

Concussion. This state is characterized by three essential features, (1) sudden loss of consciousness, (2) widespread motor and sensory paralysis of variable duration, (3) subsequent complete recovery apart from retrograde amnesia for the events leading up to the injury.

Unconsciousness occurs immediately on receipt of the blow. When the concussion is slight there is merely transitory giddiness or momentary loss of consciousness, but when more severe the unconsciousness may be prolonged. The voluntary muscles and sphincters are relaxed, respiration is shallow and rapid, the pulse is small and quick, the pupils are dilated and, indeed, every vital activity is suspended.

In rare instances concussion accompanied by no other obvious injury has proved fatal, and in these cases at autopsy the only recognizable damage has been widespread minute hæmorrhages throughout the brain.

The Mechanism of Concussion. The brain is supported, as in a water bath, by the cerebrospinal fluid inside the closed cranial cavity. This disposition of the part, protective as regards the jars and minor injuries of daily life, has its own peculiar dangers when the skull is subjected to undue violence, for the force of the impact is transmitted, according to the laws governing hydrostatic chambers, rapidly to every part of the cavity.

Formerly concussion has been attributed to a sudden deformation of the skull—a flattening in the line of the force, a broadening in the other axis—which has been thought to produce a transitory anæmia of the brain (Trotter) or a wave of pressure transmitted by the cerebrospinal fluid through the ventricles and impinging on the floor of the fourth ventricle (Duret).

The observations of Denny Brown and Russell make it necessary to modify these views. These workers have shown that in animals concussion is produced most readily if the head is not fixed, *i.e.*, is capable of being displaced at the moment of impact. From this it must be concluded that concussion is due to a sudden change in velocity (acceleration or deceleration) rather than to an increase of intracranial pressure. The velocity of the force at the moment of impact is thus of paramount importance, and if the impact is damped down by cushioning the risk of concussion is greatly reduced.

It seems probable that the actual lesion in concussion is a "molecular disturbance" of the neurones caused directly by the physical stresses due to the impact. Most of the characteristic features of concussion can be attributed to a transitory paralysis of this sort affecting particularly the hypothalamus and brain stem. Even the unconsciousness or, as he prefers to call it, parasomnia, has been attributed by Jefferson to brain stem paralysis.

Contusions and Lacerations. These injuries vary in degree up to the most severe. They are most extensive at the site of impact of the blow, and at the opposite pole, from percussion of the brain against the skull at this point (*contre-coup*). The same mechanism may lead to damage to the brain close to the dural partitions, and the nerve tissue close to the ventricles is often affected. The damaged areas become softened and disintegrated and may bleed. Blood may percolate through the meshes of the pia-arachnoid or even escape into the subdural space, but more frequently it is restricted to small areas in the brain itself.

When the damage is extensive it may give rise to focal paralytic lesions from destruction of nerve tissue, but such gross damage is unusual. Minor contusions and lacerations owe their chief danger to the coincident localized hæmorrhages and reactionary œdema of the brain. If this stage is survived, the damaged tissues may become sclerotic from neuroglial proliferation, and this sclerosis may subsequently give rise to after effects.

œdema of the Brain. The contused brain, like any other bruised tissue becomes swollen with extravasated blood and œdema fluid. In most cases the œdematous swelling is limited to the immediate vicinity of the focal lesions, but in severe injuries it may be so extensive as to cause an increase in intracranial tension and interfere with the circulation of blood and cerebrospinal fluid.

The state of "cerebral irritation" is generally attributed to œdema of the brain, though the evidence for this view is not altogether convincing. This state appears shortly after recovery from the initial concussion and may persist for a few days or considerably longer. Usually it reaches its maximum within forty-eight hours after the injury. The cerebral condition is reflected in the whole state of the patient, who lies curled up on his side, avoiding the light and resenting all interference. The mental state varies from irritability and drowsiness to delirium and even mania, the more excitable states usually supervening at night. During quiet phases there is a curious state of submerged consciousness, for although apparently insensible the patient

may respond to persistent questioning, but with a long reaction time, slowness of thought, and defective memory.

Intracranial Hæmorrhage. Intracranial hæmorrhage of traumatic origin may arise from rupture of a vessel either in the meninges or in the brain. Intracerebral hæmorrhages are very common following bruising or laceration, but they are usually small, or overshadowed by other lesions.

Extradural Hæmorrhage. Extradural hæmorrhage, though uncommon, is familiar clinically, for it gives rise to a fairly characteristic train of symptoms and signs. It follows the rupture of a meningeal vessel, often the main stem or a major branch of the middle meningeal artery, which is punctured or torn by a fracture of the inner table. The onset of bleeding is delayed by the initial collapse and low blood-pressure of the concussion period, and its progression is slow due to the adhesion of the dura mater to the bone; and for these reasons there is usually a latent period, free from pressure symptoms. Since the dura is firmly attached at the base of the skull the blood spreads principally towards the vault, and also antero-posteriorly. As the hæmatoma increases it compresses the adjacent parts of the brain and increases the intracranial tension. Its effects are at first and principally restricted to the brain close to the hæmorrhage, and only later do they become generalized. The brain abutting on the site of hæmorrhage is at first engorged from venous stasis, and is "irritable"; later, this part of the brain becomes paralysed, while a zone of "irritability" spreads progressively to other parts.

In typical cases these pathological processes may be recognized clinically. After the initial concussion and before the bleeding has progressed far, there is a latent period, free from symptoms. Then, in a few hours or, exceptionally, a few days, there develop irritative phenomena due to the venous stasis, related principally to the affected side. Later there are paralytic disturbances, at first localized, later spreading as more and more of the brain is affected (*compression of the brain*). Monoplegia, hemiplegia, or sensory loss occur, and paralysis of the palate leads to stertorous breathing. The pupil of the affected side becomes dilated, whereas its fellow, affected by the irritative zone of venous stasis, is contracted. Generalized paralytic lesions and deepening coma lead to death.

An instructive feature of the late stage of compression of the brain is the character of the pulse, which is full, bounding and of high tension. This is known as the "compression pulse." The vital centres of the brain stem must at all costs receive their proper nourishment, and to ensure this they are furnished with a remarkable compensatory mechanism. When the advancing effects of cerebral compression approach the medulla, that most delicate vital centre, the vasomotor centre, is the first to respond by becoming more susceptible to stimulation and emits impulses which lead to vaso-constriction of peripheral blood vessels. This has the effect of raising the blood pressure, and since the cerebral arteries, being independent of vaso-constrictor control, do not participate, the result is an increased flow of blood to the medulla and consequent improvement of the nutrition of the vital centres. Thus the "compression pulse" is a protective phenomenon.

Subdural and Subarachnoid Hæmorrhages. Blood may accumulate either in the subdural space or in the meshes of the pia-arachnoid. The blood may come from a meningeal artery or a venous sinus, or from veins or arteries near the surface of the brain. A common source is from one of the cerebral veins as they enter the tributaries of the superior longitudinal sinus, for these are short venous trunks passing perpendicularly from the mobile brain to the fixed dura mater. The hæmorrhage is most likely to follow a blow on the back of the head, in which the brain is suddenly thrown forwards within the cranial cavity. In blows directed from one side of the head, the brain is cushioned to some extent by the falx cerebri, and consequently is less apt to tear the veins.

Arterial hæmorrhage usually is too rapidly fatal to have much significance. Venous bleeding progresses slowly, after a free interval due to the initial shock. If the hæmorrhage is not sufficiently severe to lead to death, the blood clots, forming a hæmatoma. Small clots are absorbed, but large ones tend to persist.

Chronic Subdural Hæmatoma. Such a collection of blood clot is found most often over the parietal region, a short distance from the midline. Within a few days it becomes enveloped in membranous adhesions derived from the arachnoid mater. This membrane contains numerous reticulo-endothelial cells or *meningocytes*, which phagocytise the hæmoglobin from the blood clot, and even convert some of it into bile pigment, thus imparting a greenish-yellow or coffee colour to the affected region.

Eventually the blood clot becomes liquefied, and forms a cyst—*traumatic subdural cyst*. Such cysts are not intimately connected with the brain or dura, and may with care be shelled out. The outer parts of the cyst become organized and fibrotic, the centre becomes liquefied, and its pigment undergoes absorption. Cholesterol crystals may be deposited in large numbers. Such a cyst sometimes tends to increase in size through the accumulation of fluid, and may give rise to the signs of an intracranial tumour. Its wall may become calcified and thus be evident in radiographs.

Sequelæ of Injuries to the Brain

Any injury to the brain, from a mild concussion to severe lacerations, may occasionally be followed by untoward sequelæ. Headache, giddiness, tinnitus and ill-defined alterations in disposition are the most frequent. Traumatic neurasthenia may follow more severe injuries. It is characterized by an alteration of the mental attitude with instability, incapacity for intellectual effort, and attacks of excitement alternating with depression.

Traumatic epilepsy is a rare sequel, attributable to irritation of the motor cortex secondary to patchy gliosis in the lacerated area. Traumatic insanity is also a rare sequel which occurs in persons with an inherited tendency towards mental instability.

The relation of post-traumatic disturbances to a defect in the bones of the cranium is a problem of great importance to the surgeon. Often the headache appears to be centred round the defect; the patient has

an unpleasant consciousness of weakness at this point ; or there may be local pain, and appreciation of variations in intracranial tension, of which the normal person is unconscious. In some such cases it appears as though the defect itself is responsible for the symptoms, for closure of the gap by a bone transplant may bring relief. Usually, however, adhesion of membranes to the brain at this point and gliosis spreading deeply through the brain are the underlying factors.

In addition to the sequelæ mentioned above, there are certain complications due to rupture of cerebral nerve tracts at the time of the injury. In this category are glycosuria, polyuria (from damage to the hypothalamic region), loss of sight, hearing or smell.

Intracranial aerocele (pneumocephalus) may also occur. This rare condition is characterized by the presence of an air-containing cavity within the skull. In the common form, the aerocele lies within the substance of the frontal lobe, and it may be so large as to occupy the entire frontal lobe and extend back into the parietal lobe. In some cases, the air occupies a portion of the subdural or subarachnoid space. It may even gain access to the ventricles, either primarily or following rupture of an aerocele in the frontal lobe.

In the great majority of cases the aerocele results from a fracture of the cranium involving one of the air sinuses—the frontal sinus most often, the ethmoid, sphenoid or mastoid sinuses rarely. At the time of the fracture the subjacent dura mater and arachnoid are torn, and a narrow track is formed leading from the air sinus into the brain. When the patient coughs or sneezes (or swallows, in the case of the mastoid air cells), the increased pressure within the sinus forces air into the substance of the brain.

In a few cases the bone defect has been caused by inflammatory erosion of the sinus wall, for example, in mastoiditis or ethmoiditis. It is possible that occasionally an aerocele may result from the action of gas-forming organisms, for example, in a brain abscess.

An intracranial aerocele generally develops several days, or even a few weeks, after injury. In the common frontal type it is associated with repeated sneezing and sometimes with the discharge of cerebrospinal fluid from the nostril. As the aerocele increases in size the intracranial tension rises, and leads to headache, vomiting, drowsiness or delirium, and finally coma. In 50% of cases the issue is fatal, either from intracranial pressure or from superadded infection.

Injuries to the Skull and Cranial Nerves

The skull may be fractured at the site of impact of a blow, from its direct violence, or at some distant part from secondary stresses set up in the bones. The nature and extent of the fracture depend upon the size of the injuring object as well as upon the magnitude of the force.

A small object inflicts a localized fracture at the point struck. The fracture may be compound, comminuted or depressed, and it may be given various descriptive names—indentation, pond, gutter, punctured, etc. Such fractures are commonest in the vault of the skull. Rarely a pointed object may pass through the mouth or nose and cause a direct fracture of the base or pass through the orbit and lead to damage

of the orbital plate. Where such an injury is caused by an object of small calibre, the wound of entry may be so slight as to escape the most careful inspection.

A large object, inflicting violence over a wide area of the skull, damages it by a different mechanism. There may be local damage at the site of impact, but, in addition, abnormal stresses and strains are set up through the whole skull. The base, the least elastic portion, gives way first, and fissures appear, which may extend widely, usually in a transverse direction or obliquely. Not infrequently the fissures radiate in several directions, and they may cross the mid-line at the base.

The cranial nerves may be injured in fractures of the base of the skull, particularly of the anterior and middle fossæ. Nevertheless, it is remarkable how often the nerves escape injury, even in very extensive fractures. Often the line of fracture avoids the nerve foramina, which are surrounded by dense bone and so are relatively resistant. Fibres of the olfactory tract may be torn in an injury to the cribriform plate; the optic nerve is liable to be damaged as it lies in the optic foramen; injury to the petrous bone may rupture the abducent nerve; the facial and acoustic nerves may be injured as they lie in their bony canals.

Healing of a fracture in the membrane bones of the skull takes place by fibrous union. Usually bony union does not take place, and there is no formation of callus at the seat of fracture. Occasionally, after a long interval, there is a certain amount of ossification between the fragments where the fracture crosses a suture line, but the new bone is always very scanty. The lack of new bone formation is generally attributed to the fact that osteoblasts are absent from the bones formed in membrane. Similar failure of ossification occurs at the site of a trephine opening, the edges of which remain clearly defined and little altered after a period of years.

INTRACRANIAL SUPPURATION

The intracranial infections of surgical interest include extradural abscess, certain forms of meningitis, thrombophlebitis of the venous sinuses, and brain abscess. These conditions differ greatly in their pathological features, and when they occur singly they give rise to distinctive clinical effects. Often, however, two or more of them occur together, or arise consecutively in the course of an extra-cranial suppuration, and in such cases the clinical picture is correspondingly confused.

Primary Sources of Infection. In the great majority of cases intracranial suppuration is a sequel to a local septic process. Most often it follows suppurative otitis media or infection of the nose and paranasal air cavities, or it may arise as a complication of a compound fracture of the skull. Not infrequently it is due to spread of infection from a septic focus in the lip, nostril, or orbit. Rarely intracranial suppuration follows infection from a distant septic process. Intrathoracic infections such as bronchiectasis or pulmonary abscess are especially apt to involve the brain, presumably owing to the ease with which

septic emboli set free in the pulmonary veins may be transported to the cerebral arteries.

Pathways of Infection. Infection may reach the intracranial structures by any of three routes, viz. :—

- (1) By continuity of tissue.
- (2) By the blood stream, arterial or venous.
- (3) By special regional pathways.

It is important to note that lymph vessels offer no route of access to the brain. The brain has no lymph vessels, and the cerebrospinal fluid occupies a closed system, cut off from neighbouring lymph spaces by the endothelial lining of the meninges. It is now known that even the perivascular spaces in the brain are not lymph vessels, but extensions of the subarachnoid space, and so also are the perineural spaces of the olfactory and optic nerves.

(1) *By Continuity of Tissue.* This is one of the most important pathways. In a recent investigation by Logan Turner and Reynolds it was held responsible in 40% to 50% of cases.

Infection by this route is common in otitis media, and also in compound fracture of the skull. An extradural abscess is the commonest result, and if the dura mater is intact the infection generally spreads no further. If the dura mater is damaged, however, or if it undergoes inflammatory softening, further spread by direct continuity may lead to meningitis or to an abscess in the brain. Even if the dura is intact, however, the infection may spread through the wall of a vein, and lead to sinus thrombosis.

(2) *By the Blood Stream.* Infection may reach the brain by the arterial blood stream, either in conditions of general pyæmia or, rarely, following erosion of the internal carotid artery by a septic process in the neck. In such cases, the usual result is the formation of single or multiple brain abscesses, often accompanied by meningitis.

A much more important route, however, is the venous blood stream. This pathway was partly or wholly responsible in over 40% of the cases examined by Logan Turner and Reynolds. The process is a septic thrombosis, which originates in minute venules at the primary focus, and spreads, either in the normal direction of blood flow or against it, to the large intracranial venous sinuses. Infection by this route is not uncommon in otitis media, when the lateral sinus is especially liable to involvement. In this way also the cavernous sinus is infected from a septic focus in the lip, nostril or orbit (*see p. 274*).

(3) *By Special Regional Pathways.* The most important pathway in this category is that of the perineural olfactory sheaths. These sheaths enclose endothelium-lined spaces which communicate with, and indeed are a part of, the subarachnoid space of the anterior cranial fossa. In health the perineural spaces do not communicate with the lymph vessels of the nose, but if, as a result of fracture of the anterior cranial fossa, or of ill-advised operation upon the roof of the nose, the olfactory sheaths be laid open, they afford immediate access for infection. Usually in these cases the result is meningitis, less commonly an abscess in the brain.

Other special regional pathways, which occasionally transmit infec-

tion, are the pial sheaths of the optic, auditory and vestibular nerves. Rarely a persistent cranio-pharyngeal canal (Rathke's pouch) has been observed to act similarly as a pathway for infection.

Extradural Abscess. This is attributable almost invariably to spread of infection from some local lesion. Most often it follows suppurative otitis media or infection of the mastoid air cells, or it may occur as a complication of compound fracture of the skull, osteomyelitis of the cranial bones, or infections of the scalp.

In the common form secondary to ear disease the abscess cavity is of small size, contains very little pus, and is surrounded by an exuberant mass of granulation tissue, which lies between the dura mater and the bones of the skull. The abscess gives rise to constitutional effects, but since its size is small there is rarely evidence of increased intracranial tension or of focal lesions from pressure on the brain. Sometimes, however, papilloedema (optic neuritis) occurs.

Extradural abscesses following compound fracture vary in severity with the virulence and the variety of the infection. Not infrequently they appear several weeks after the injury and grow slowly to large size, giving rise to increasing toxæmia and to signs of an increased intracranial pressure. If the infection is virulent, and particularly if the dura mater has been damaged at the time of fracture, the leptomeninges may become involved.

When the skin over an extradural abscess is unbroken, there sometimes develops a hard, tender, localized swelling of the soft parts (Pott's puffy tumour), an inflammatory oedema comparable to that seen superficial to any acute suppurative process, and without other pathological significance.

An extradural abscess may resolve, but if untreated is apt to extend beyond the reactive zone of granulation tissue and to lead to subdural infection, leptomeningitis or abscess in the brain.

Acute Leptomeningitis. This may, like extradural abscess, follow local infective lesions, or it may follow infection from some distant source. The latter type, exemplified in meningococcal meningitis and in the meningitis of pneumonia, septicæmia or other disease, does not require consideration here.

Local infection of the leptomeninges is most likely to arise where the dura mater has been damaged, as in a compound fracture or by a penetrating wound, but it may occur with the dura mater intact. The condition is grave, for the whole subdural space is usually invaded. Occasionally, however, if the infection is less virulent, adhesions form and lead to resolution of the disease or to a localized subdural abscess.

Thrombophlebitis of the Venous Sinuses. This is a grave and often fatal affection. The channel most often affected is the *lateral sinus*, which owes its susceptibility to its close relation to the middle ear. The disease usually follows osteomyelitis of the mastoid bone secondary to otitis media, and the sinus may be infected by direct continuity or along one of its small tributary veins. As a result of the infection the endothelial lining of the sinus becomes inflamed and thickened, and thrombosis occurs, blocking the lumen. The thrombus being infected

undergoes suppuration and softening, and consequently is very apt to break down and to cause general pyæmic dissemination. The thrombosis may extend down the internal jugular vein, which may then be felt as a firm tender cord in the upper part of the neck. Abscesses may form in the soft tissues around the vein, and the cervical lymph glands are enlarged and tender. The infection may spread in other directions and lead to meningitis and cerebral abscesses.

The *cavernous sinus* may be infected from the lateral sinus, or from septic lesions in the soft tissues of the face or orbit, by thrombosis spreading along the angular vein or by way of the pterygoid venous plexus. It is to this complication that insect bites, erysipelas, boils and carbuncles in the region of the upper lip and cheek owe their especial danger. Since the two cavernous sinuses are directly connected across the mid-line the infection rapidly becomes bilateral. Obstruction of the venous pathway and the local effect of the intense inflammation combine to cause great congestion and œdema within the orbit and in the eyelids and face. The infection may lead to paralysis of the third, fourth and sixth cranial nerves, which lie in, or in the wall of the sinus, and thus give rise to ptosis, squint and ophthalmoplegia. The infection tends to spread along communicating venous channels, and in all but a few cases is rapidly fatal.

The *superior sagittal sinus* is only rarely affected, and then usually from septic processes in the skull or scalp. Its pathological features do not differ from those seen in other sinuses.

Abscess of the Brain. An abscess in the brain may be due to direct bacterial invasion from some local suppurative process or to hæmatogenous infection from some distant source. The former is by far the commoner mode of origin.

Abscesses due to local suppuration are most often attributable to disease of the middle ear, and the abscesses are situated in those parts of the brain that lie nearest to the primary focus, namely, the temporal lobe or cerebellum. An abscess in the temporal lobe is usually situated in the white matter of the centrum ovale. It is generally attributable to spread of the infection through the tegmen tympani, and there is often extradural and subdural suppuration in the same region. In other cases there is no evidence of direct extension, and it may be presumed that the infection has been carried along communicating veins. A cerebellar abscess, which usually lies on the same side as the diseased ear, is often secondary to phlebitis of the sigmoid portion of the lateral sinus, to which it is closely related.

Much less often the cause of the abscess is to be found elsewhere than the middle ear. Suppuration of the frontal sinuses occasionally leads to abscess in the frontal lobe, and rarely septic osteomyelitis of one of the skull bones has a similar sequel. Injuries to the skull and brain provide a portal of entry for organisms, or infection may be introduced at the time of injury, and if foreign bodies such as portions of clothing or fragments of shrapnel are also introduced an abscess is especially likely to occur.

The character of the abscess depends upon the virulence of the infection. If acute, the abscess is ill-defined, and is more correctly

regarded as a spreading suppurative encephalitis. A chronic abscess, which is more common, becomes surrounded by a capsule of firm fibrous neuroglial tissue, and may remain latent for many weeks. The abscess is usually single, and of small size. Its purulent content is usually thick, foul, and of greenish-yellow colour, but it may be dark brown from admixture with broken-down blood clot. Staphylococci, streptococci or pneumococci may be present, but often the pus appears sterile when tested by ordinary cultural methods.

Metastatic abscesses, due to hæmatogenous infection, are not infrequent in the course of general pyæmic and septicæmic states, and are then usually small and multiple. Abscesses may, however, occur quite apart from general pyæmia, and in cases where there is no other evidence that the infection has gained the blood stream. This occurs most often as a complication of intrathoracic suppurative diseases, bronchiectasis, abscess of the lung, or chronic empyema, and it constitutes one of the risks of operations on infective lesions within the thorax. It seems likely that the special relationship of thoracic disease to brain abscess may be explained simply upon the anatomy of the circulation, for minute infected particles set free in the pulmonary veins pass directly to the systemic circulation. Not infrequently, abscesses following thoracic disease are single. They are situated most often in the cerebrum, and since the infection is virulent they usually progress rapidly to a fatal issue, often by rupture into the ventricles.

INTRACRANIAL TUMOURS

Intracranial tumours include tumours arising from the brain itself, from its membrane, from the pituitary gland or from the acoustic nerve, as well as some rare varieties. Tumours from these sources vary greatly in their morphology, incidence, and life history. Many are rapidly growing, infiltrating tumours, unresponsive to any form of therapy, however early and intensive; others, on the contrary, grow slowly, and are amenable to surgical treatment.

The work of Cushing and his associates has done much to dispel the earlier fatalistic attitude towards brain tumours. An intracranial neoplasm does not now inevitably presage death, and in an appreciable proportion of cases a complete eradication may be accomplished.

Of this latter group the outstanding example is the meningioma, which if accessible may, by the exercise of great care, be extirpated completely and with safety. Tumours of the acoustic nerve also may be removed, though the operation has its special dangers. Some of the tumours of the glioma group react well to palliative measures, so that the fatal issue may sometimes be postponed for many years.

It is of obvious importance to have a full appreciation of the various types of intracranial tumour and of the secondary disturbances which they may set up. These naturally vary in form and degree, but all types of growth tend, from their situation within the cranial cavity, to have certain effects in common. In general, they may affect (1) the brain, whether by compression, invasion, irritation, hæmorrhage or œdema; (2) the intracranial circulation, of blood or cerebrospinal fluid; (3) the skull, by erosion or invasion, and (4) the spinal cord, by

descending degenerations of the nerve tracts. A few tumours may, in addition, affect the meninges, by invasion or implantation. Rarely, the more malignant forms may invade even the soft parts outside the skull, and this is especially apt to occur after a decompression operation. Intracranial tumours practically never metastasize.

The relative frequency of different varieties of tumours is indicated by Cushing's statistics, taken from an extensive series of 1,146 cases. In 43% of these, the tumour originated in the brain itself (various types of glioma, including "gliosarcoma" and "sarcoma"), 19% were pituitary tumours, 12% meningiomata and 9% tumours of the acoustic nerve. Miscellaneous tumours, including congenital and metastatic growths, made up the remaining 17%.

MENINGIOMA (Dural Endothelioma)

A meningioma is a simple tumour of slow growth, which is dangerous to life only by reason of its situation in the closed cranial cavity. It grows from the arachnoid mater (not, as was formerly



FIG. 117. Meningioma (dural endothelioma). The tumour, derived from the arachnoid mater, has compressed and indented the brain but has not invaded it. Note the lobulated character and the vascularity of the growth. (After Cruveilhier.)

believed, from the dura mater), and it seems probable that in most cases it originates from the arachnoideal villi which lie in relation to the large venous sinuses (*see* p. 263).

A meningioma is situated most often in the anterior and middle fossæ and on the superolateral surfaces of the brain. By reason of its slow growth, which permits compensatory changes in the bulk of the

brain, it may attain considerable size, and at the time at which operation is performed it may be the size of a golf ball or even larger. Often the tumour is closely related to one of the large venous sinuses of the meninges, and often it is extremely vascular. Moreover, the vessels in the meninges and bone near the tumour are frequently dilated, and consequently hæmorrhage at the time of operation may be profuse. Occasionally the tumour is less vascular and more fibrous, and it may then become calcified (*psammoma*).

A meningioma may extend deeply towards the brain or superficially through the dura mater and the skull. In extending deeply it displaces the brain but never invades it, and consequently when accessible it may, by the exercise of patience and care, be enucleated entire. Sometimes it is sessile, and is attached to the arachnoid mater by a broad base, but even when pedunculated and almost buried in cerebral tissue it always retains a definite capsule. The dura mater superficial to the tumour is first thickened by reactionary fibrosis and later invaded, and eventually the cranial bones also are affected.

The effects of a meningioma upon the overlying cranial bones are characteristic and important. The bone is sometimes invaded by tumour cells, but more commonly it undergoes changes from perineoplastic hyperæmia. At first there is a simple erosion, so that a cup-like depression, sometimes bounded by projecting osteophytes, appears on the inner table. Later there is often some reactionary new bone formation on the outer table, forming a hard, smoothly rounded swelling under the scalp. Less often bone is formed in perpendicular deposits which resemble the "sun-ray" spicules of periosteal sarcoma. Seen in a radiogram, such an appearance is apt to suggest the presence of a primary bone tumour, and the underlying meningioma may escape recognition.

Microscopically, a meningioma is composed of elongated, spindle-shaped cells, somewhat resembling fibroblasts, set in a matrix containing collagen fibrils and hyaline material. Commonly the cells

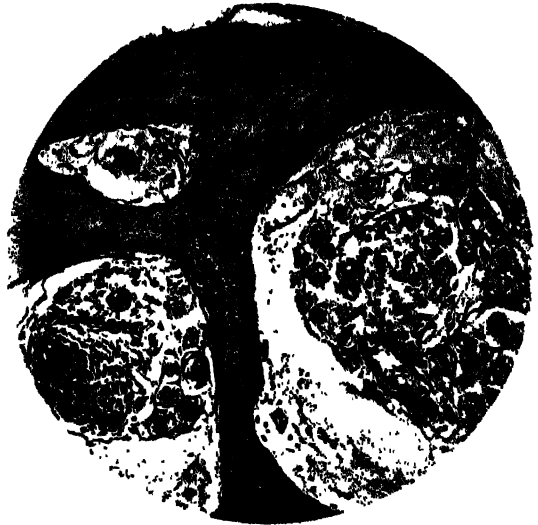


FIG. 118. Meningioma (dural endothelioma) penetrating the skull. $\times 100$. The tumour is composed of solid masses of cells arranged in whorls. The cells have the general character of endothelial cells. Near the centre of the whorls they are somewhat spindle shaped, and in other parts they are larger and more rounded.

(Laboratory of Royal College of Physicians of Edinburgh.)

have a whorled arrangement, often around a central blood vessel. Larger cells of endothelial type may be present. Often the blood vessels are large and numerous, and there may be areas of hæmorrhage. In some of the less vascular tumours there are spherical bodies composed of concentric laminae infiltrated with calcium (*psammoma bodies*).

The course of a meningioma is characterized by slow and, for the most part, symptomless growth. In approximately half of the cases there is a history of an injury, often definitely localized to the affected part of the skull. The first and for a long time the only sign may be some local disturbance, such as pain of a dull aching character localized to the affected region, or unilateral headache. Sometimes the inward growth of the tumour may give rise to focal signs such as epileptiform convulsions or, if the tumour lies at the base, an ocular paresis. In other cases the presence of a bony swelling under the scalp may be the revealing sign. In radiograms the changes described above may be recognized, and, in addition, if the tumour is very vascular it may be possible to see dilated vascular channels in the bones.

THE GLIOMA GROUP

This term has been applied to the tumours hitherto called gliosarcoma and sarcoma and to other lesions, as well as to the simple form of glioma, for it is now recognized that all these tumours, whatever their appearance and behaviour, are derived from the cells of the supporting fabric of the brain, the neuroglia. The neuroglia, like the actual nerve cells, is an ectodermal structure, and it is therefore incorrect to label its tumours sarcomata. True sarcoma is extremely rare, for practically the only mesodermal tissues in the skull are the blood vessels and their supporting framework.

In the past two decades there have been many additions to our knowledge of the pathology and life history of gliomata. On the one hand, improvements in the staining methods applicable to nerve tissues, which have been introduced especially by members of the Spanish school of neuropathologists, have rendered possible an accurate appreciation of the histology of brain tumours, and, on the other hand, the widespread adoption of surgical measures in this field has given a great impetus to fuller investigation.

Classification of Gliomata

Bailey and Cushing have emphasized that in brain tumours, as in tumours elsewhere, the more primitive the predominating cell the more malignant is the tumour's behaviour. Tumours composed of cells resembling adult neuroglia cells are slow-growing, and but for their peculiar situation would be non-malignant; tumours composed of primitive cells grow fast and kill rapidly. The cells of the neuroglia in their development in the embryo undergo many changes of shape, form and staining reaction, and in tumours the cells may revert to any of these primitive forms. Thus it is possible to classify a tumour according

to the degree of reversion of its predominant cell type, and the greater the reversion the more malignant the tumour.

This is the rational basis of Cushing's classification. It has evoked much adverse criticism on various pathological grounds, and particularly on the grounds that few brain tumours conform strictly to type, many show several different stages of cell differentiation, and many cannot be classified exactly in any of the recognized groups; but in spite of these criticisms there can be no doubt that the classification represents a great advance upon any previously attempted. For a proper understanding of its basis it will be necessary to consider briefly the development of the neuroglia.

Development of Neuroglia. Practically all the tissues of the central nervous system are derived from ectoderm. At the dorsal surface of the early embryo there appears a raised "neural plate," and this is hollowed out as the "neural groove," and later depressed below and completely separated from the skin surface. This is the primitive brain and spinal cord, and at this stage it is represented by a tube, lined by a single layer of epithelial cells derived from the surface ectoderm, the *neural or medullary epithelium*. Rarely the cells of a tumour revert to this primitive type, and the tumour is correspondingly malignant (the so-called medullary epithelioma).

From this medullary epithelium there develop both the nerve cells proper and the supporting framework or neuroglia. The nerve cells and their immediate progenitors so rarely give rise to tumours, that their development need not be considered further. Almost all brain tumours arise from glial tissues, and the development of the glia must therefore be studied in more detail. The primitive neuroglia cell is the *spongioblast*, an elongated, somewhat spindle-shaped cell that can be identified by its staining reactions with gold sublimate. Cells of this type are frequently seen in the common malignant glioma (gliosarcoma), and this tumour may therefore be called a *spongioblastoma*.

From this spongioblast stage the developing neuroglia cell undergoes various modifications and eventually attains the adult form, the *astrocyte*. This is a star-shaped cell with long branching spidery processes, one of which, the "sucker-foot," is attached in close relation to a capillary blood vessel, whence its nourishment is derived. Astrocytes predominate in the simple glioma, which may therefore be called an *astrocytoma*. Two types of astrocyte are recognized, protoplasmic astrocytes and fibrillary astrocytes, and either may predominate in a simple glioma or astrocytoma.

One further cell requires to be mentioned—the *indifferent cell* or *medulloblast*. This is a small, round or carrot-shaped, dark-staining cell. Its origin and function are not clear, but it seems probable that it is derived from an original cell of the medullary epithelium, and that it is bipotential, able to form either nerve cells or neuroglia. It is consequently of primitive type, and its tumours, which arise most often in the cerebellum, are exceedingly malignant (*medulloblastoma*).

Lastly, there are two other structures from which tumours may occasionally arise, the pineal gland and the ependyma or lining mem-

brane of the ventricles. Both of these tissues arise from spongioblasts at an early stage in the development of the brain, and the tumours arising from them may be regarded as gliomata with special characteristics.

Types of Glioma

The common tumours of the glioma group fall into three classes, distinctive both in morphology and clinical course. Formerly they



FIG. 119. Glioma of the cerebral cortex. The tumour has extended to the surface of the brain and has compressed the lateral ventricle.

(Department of Surgery, University of Edinburgh.)

were known respectively as glioma, gliosarcoma and sarcoma. Since "sarcoma" is inadmissible for tumours of ectodermal origin it is proper that these terms should be superseded, but it is by no means easy to replace them. The following classification may be adopted :—

- (1) Glioma of slow growth : astrocytoma (simple glioma).
- (2) Glioma of rapid growth : spongioblastoma (gliosarcoma).

(8) Glioma composed mainly of small round cells : medulloblastoma (sarcoma).

In addition, there are rare tumours arising from the pineal body, the ependyma, and other tissues.

(1) Glioma of Slow Growth : Astrocytoma (Simple Glioma). This tumour is composed mainly of adult neuroglia cells or astrocytes. It is the commonest neuroglial tumour, and it is relatively benign in the pathological sense and of slow growth. It occurs at any age and is

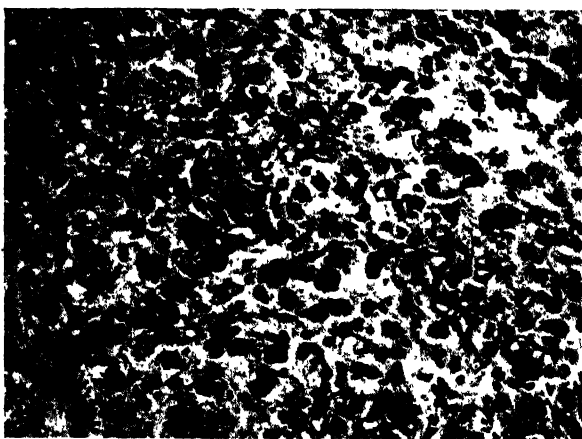


FIG. 120. Astrocytoma. Small star-shaped cells and many larger cells of protoplasmic type are seen. The fibrillar processes are evident.
(*Department of Pathology, University of Glasgow*)



FIG. 121. Glioma arising from the roof of the fourth ventricle. The tumour has displaced the cerebellum and has given rise to a considerable degree of hydrocephalus.
(*Department of Surgery, University of Edinburgh.*)

common in the frontal lobes and in the cerebellum, less frequent in the other parts of the cerebral hemispheres. In adults the frontal lobes are affected most commonly, whereas in children the cerebellum is the commonest site. The tumour forms a fairly firm mass of indefinite outline, merging indistinctly into the surrounding white matter of the brain. It is usually pale and relatively avascular, and is therefore liable to central degeneration from necrosis. This may proceed, especially in the cerebellum, to the formation of a *gliomatous cyst*, a rounded, smooth-walled space of considerable size, containing clear straw-coloured fluid. Sometimes the cyst may replace almost the whole tumour, and only a few tumour cells remain in the cyst wall.

Microscopically, the tumour is composed principally of adult astrocytes, which are recognizable in sections prepared by the gold sublimate or other suitable methods as star-shaped cells with elongated branching processes. The intercellular substance varies in amount and may be clear or traversed by numerous fibrils. Vessels are few and well formed, and mitotic figures are scanty. The whole appearance often may resemble adult neuroglia tissue and it may sometimes be difficult to distinguish the tumour from the surrounding white matter.

Tumours of this class are of slow growth, and if the dangers of increased intracranial tension are overcome by a timely and suitably placed decompression opening, the fatal issue may be postponed for a considerable number of years. In Cushing's series the average survival period was almost six years.

(2) **Glioma of Rapid Growth : Spongioblastoma (Gliosarcoma).** This tumour, almost as common as the first type, differs greatly in appearance

and behaviour. Its predominant cell is the spongioblast, the most immature cell of the neuroglia series, and the tumour is correspondingly malignant. It commonly affects adults between the ages of forty and fifty, but may occur at any age from ten to seventy years. The frontal lobes are the most commonly affected, less often other parts of the cerebrum. The tumour forms a bulky soft vascular mass, very liable to hæmorrhage and to central necrosis. It invades the surrounding cerebral tissue and destroys it. Often the



FIG. 122. Malignant glioma (spongioblastoma).
 × 275. The tumour is derived from glia and it reproduces the primitive neuroglia cells or spongioblasts, large, darkly staining, spindle-shaped cells terminating at one or both poles in wavy processes.
 (Laboratory of Royal College of Physicians of Edinburgh.)

tumour appears to be encapsuled, but this appearance is misleading, for the capsule, which consists of brain tissue compressed by the rapidly growing tumour, itself contains malignant cells. The tumour usually does not invade the meninges, but in rare cases after an exploratory operation it may extend and involve the soft tissues of the scalp and neck. It does not metastasize to distant parts. A most important effect of the tumour is to give rise to widespread vascular changes and oedema in the brain. This oedema is one of the important factors leading to the early fatal issue.

Microscopically, the tumour is very cellular, and very pleomorphic. There are round and spindle-shaped cells of various sizes, so that the growth resembles a

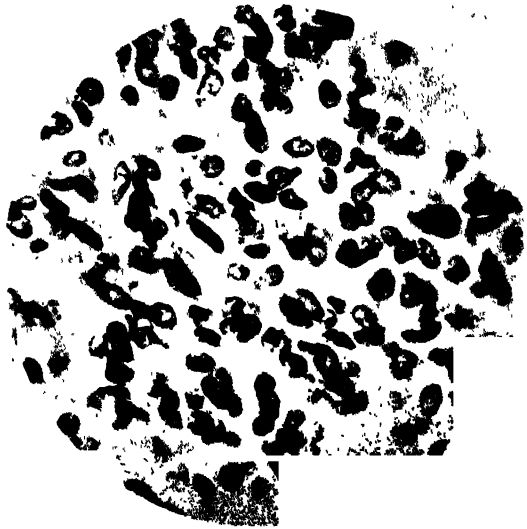


FIG. 123. Medulloblastoma. $\times 400$. A malignant tumour of the cerebellum, derived from neuroglia, and reproducing primitive glia cells of medulloblast type.

(Laboratory of Royal College of Physicians of Edinburgh.)

rapidly growing mixed-cell sarcoma. Often giant multinuclear cells are present, and there may be syncytial masses. Mitotic figures, often irregular in form, are common. The tumour is very vascular and there are usually areas of degeneration and hæmorrhage. The high malignancy of the tumour is reflected in the post-operative survival rate, which in Cushing's series averaged twelve months. Decompression relieves the intracranial tension but has little effect on the cerebral oedema, and operation, therefore, often gives little benefit.

(3) **Glioma composed mainly of Small Round Cells : Medullo-blastoma (Sarcoma).** This tumour, the third member of the glioma group, is much less common than those already described, and it has been recognized as a distinct type only through the work of Bailey and Cushing. It seems probable that formerly it was often regarded as a small round-cell sarcoma. It is a tumour of childhood, and almost always arises in the cerebellum, either in the vermis or in one of the lateral lobes or in the roof of the fourth ventricle. The tumour has a remarkable tendency to disseminate along the meninges, and numerous secondary growths may cover the surface of the hind-brain (sarcomatosis of the meninges), often obscuring the primary lesion. It is a rapidly growing tumour, and, from its position close to the fourth ventricle, it is very apt to cause hydrocephalus by obstructing the cerebral aqueduct. The tumour is very responsive to irradiation, and adequate exposure to X-rays or radium may effect a remarkable relief of pressure symptoms.

Microscopically, it is very cellular. The cells are small, and round or carrot shaped, with deep-staining nuclei and scanty cytoplasm, and in its whole appearance it resembles a round-cell sarcoma. Occasionally there is a rosette-like arrangement. The cells are believed to be medullo-blasts or "indifferent cells," the primitive bipotential cells derived from the medullary epithelium.

TUMOUR OF THE ACOUSTIC NERVE

This tumour differs both in its nature and in its effects from either of the groups of intracranial tumours already considered. It arises from the acoustic nerve, from either its cochlear or vestibular fibres, and is a neurinoma derived from the neurilemma sheath (*see* p. 818). Not infrequently there are bilateral tumours. In rare cases one of the various forms of neurofibromatosis coexists.



FIG. 124. Acoustic neuroma. $\times 275$. The tumour is composed of leashes of spindle-shaped cells resembling the cells of the neurolemma sheath.

(Laboratory of Royal College of Physicians of Edinburgh.)

The tumour is of slow growth, benign and encapsuled, dangerous only from its close proximity to important structures. The tumour arises usually in that part of the acoustic nerve which lies immediately outside the main cranial cavity in the internal acoustic meatus. It forms a fibrous, grey or greyish-yellow mass, firm and solid at first, though later with small areas of degeneration at the centre. The nerve fibres do not traverse the tumour,

neither are they spread over its surface, but are completely engulfed and lost. The tumour slowly dilates the internal acoustic meatus and protrudes into the cranial cavity so that it lies in the angle between the pons and the cerebellum, forming a more or less oval mass which may attain a long diameter of 3 to 5 cms. As the tumour arises deep to the point at which the nerve pierces the dura, it is invested in a capsule of arachnoid. In its expansion it encroaches upon the major branches of the basilar artery, which becomes incorporated in the capsule. Hæmorrhage from one of these vessels constitutes a formidable risk at operation. Situated as it is in the confined subtentorial cavity, the tumour, even when small, causes much damage by impinging on adjacent structures. Neighbouring nerves are stretched

and paralysed, the cerebellum is affected, and, most important of all, the pons is dislocated far from its central position, compressing and obstructing the cerebral aqueduct and leading to hydrocephalus.

Microscopically, the tumour is composed of interspersed zones of dense and of lax connective tissue. In the dense areas elongated or spindle-shaped cells are buried in a dense interlacing fibrous stroma. The cells are for the most part scanty and scattered diffusely, but they may be numerous and arranged in whorls. The nuclei usually present a palisade arrangement. Interspersed irregularly in small patches are areas of lax connective tissue with a loose reticular and almost myxomatous appearance.

The effects of the tumour are characteristic, and are clearly reflected in a striking chain of clinical features. For a long time the only effect is interruption of the fibres of the two divisions of the acoustic nerve, and either the cochlear or the vestibular division may be affected first. There is therefore a history that for a period of years there has been progressive unilateral deafness, often with tinnitus and some giddiness.

As the tumour expands the internal acoustic meatus, and begins to encroach upon the cranial cavity, it may cause pain, of a dull, aching character in the suboccipital region and below the ear.

With further increase in size the tumour affects other cranial nerves, which become stretched out by the dislocation of the mid-brain towards the opposite side. The trigeminal nerve is usually the earliest to be affected and there may be numbness or a sensation of burning in the field of its distribution. Involvement of the facial nerve may later lead to some degree of facial paresis. The abducent nerve, though close to the site of the tumour, escapes damage at first on account of its length, which allows a certain degree of stretching. Later, however, its involvement leads to diplopia and strabismus.

Further enlargement leads to pressure upon the cerebellum, with ataxia and nystagmus. Most important of all, even a small tumour of the acoustic nerve may dislocate the mid-brain sufficiently to cause obstruction of the cerebral aqueduct, and may form a "pressure cone" by forcing the brain stem into the foramen magnum; and with the onset of internal hydrocephalus there arise all the signs of increased intracranial pressure. The nystagmus is increased, vomiting of the cerebral type occurs, and there is an extreme degree of papilloedema.

UNCOMMON INTRACRANIAL TUMOURS

Angioma. An angioma in the brain is situated most commonly in the cerebellum. It is a congenital tumour and may be associated with angiomas in other parts of the body or with other congenital malformations, and it may have a familial incidence.

Cushing and Bailey divide angioma of the brain into two major groups, the angiomatous malformations and the true neoplasms or angio-blastomata.

(1) **Angiomatous malformations** are developmental in origin and are sometimes associated with congenital naevi of the scalp. They

may be venous or arterial in character, rarely capillary. The dilated vessels are situated on the surface of the brain, generally over one cerebral hemisphere. There may be a simple enlargement of a single vessel, a tangled varicosity of several vessels, or a complicated racemose dilatation extending widely over the surface and also deeply into the substance of the brain.

Such malformations may give rise to attacks of Jacksonian epilepsy, to unilateral exophthalmos and to increased intracranial tension with papilloedema. An arterial angioma, or a venous one that has acquired secondary communication with the arterial system, may give rise to

a bruit, which, though not so loud as that caused by an arterio-venous aneurysm, may yet be distinctly audible with a stethoscope.

(2) The angioblastoma is a true tumour composed of cells of angioblastic origin. It is situated almost always in the cerebellum, generally near the midline close to the posterior end of the fourth ventricle. It may be solid or cystic. Three types are recognizable on microscopic examination, according as the structure is mainly capillary, mainly cellular or mainly cavernous. In its



FIG. 125. Ependymal glioma. $\times 275$. The tumour is derived from neuroglia cells and reproduces the primitive structure of the ependymal lining membrane of the ventricles. Some of the cells are arranged in palisade fashion round a semilunar space. Near the left margin is a pseudo-rosette.

(Laboratory of Royal College of Physicians of Edinburgh.)

clinical course, it resembles closely and is mistaken sometimes for simple glioma.

Dermoid Cyst. A dermoid cyst inside the cranium is rare. It may arise either in the brain, especially in the cerebellum, or in the subdural or epidural space and may grow slowly and eventually attain large size. Occasionally an extradural dermoid cyst communicates through a small aperture in the bone with a cyst in the soft tissues of the scalp or face, especially at the external orbital margin.

Tumours of the Pineal Gland. These are of the nature of gliomata or teratoma. Both varieties affect young adults, usually of the male sex. They do not grow rapidly, but from their situation may tend even when small to obstruct the cerebral aqueduct and to lead to hydrocephalus. The first signs, and often the only ones, may be those of increased intracranial tension. Sometimes, and especially

in the case of a teratoma, there is some degree of sexual precocity, which is believed to be due to an increased functional activity of the gland.

Tumours of the Ependyma. The ependyma, the lining membrane of the ventricles, is derived from spongioblasts, which early in their histogenesis become differentiated from the cells destined to form the neuroglia. Ependymal cells are characterized by the possession of cilia and tiny, rod-like, deep extensions of their protoplasm—blepharoplasts. Both these characteristics may be reproduced in the tumours. Ependymal tumours occur usually in relation to the fourth ventricle. They are of slow growth but lead rapidly to obstructive hydrocephalus. They may be found, rarely, in other parts of the ventricular system.

Sarcoma. It seems probable that a true primary sarcoma in the brain is of extreme rarity, and that the majority of tumours previously regarded as of that nature are gliomata. A true malignant mesoblastic tumour may arise from the perivascular connective tissue. Occasionally a sarcoma in some other part of the body may metastasize to the brain.

Tuberculoma. This is a tuberculous mass, either a solitary follicle or, more commonly, several confluent nodules. It occurs most often in children, and usually affects the cerebellum or the frontal lobe, and forms a lump which at first is firm and rounded, but later caseates. It may attain the size of an egg, and, especially when situated in the cerebellum, gives rise to clinical features which may simulate those of a tumour. It commonly leads to a fatal issue by infecting the meninges.

Gumma. A gumma originates in, or close to, the meninges as single or multiple nodules. The nodules are grey or greyish red, and, in their progress, they resemble gummata elsewhere. They tend to undergo central softening and, later, to heal with the production of much scar tissue and with serious cerebral impairment.

EFFECTS OF INTRACRANIAL TUMOURS

The symptoms of intracranial tumours fall naturally into two groups—those due to the local effects of the tumour upon the adjacent brain and membranes, and those which result from an increase of intracranial tension.

Those of the first group are the focal symptoms, which vary with the situation and character of the individual tumour. Their consideration would include the whole subject of topographical diagnosis, which is outside the scope of the present work.

The second group includes the classical triad, headache, vomiting and papilloedema (optic neuritis), and also giddiness, convulsions, changes in mentality, and the signs characteristic of hypopituitarism.

Headache may be due either to localized pressure of the tumour or to a general increase in the intracranial tension. Local pressure pain is most characteristic of meningioma, or it may occur when an acoustic nerve tumour expands the auditory meatus. The pain is

usually localized to one side of the head or even to a particular spot, and, in the case of a meningioma, there may be tenderness on pressure. Subtentorial tumours sometimes give rise to pain referred to the nape of the neck. Headache from increased intracranial tension is most severe with tumours that lead to internal hydrocephalus, such as tumours of the acoustic nerve, the cerebellum and the fourth ventricle. The pain is paroxysmal, worst at night and in the early morning, and is precipitated by any action, such as coughing, straining, or pressure upon the veins of the neck, which will lead to an increased tension inside the skull. Cerebral oedema is probably an important cause of headache.

Vomiting, like headache, is most frequent at night and in the early morning. It is probably due to increased intraventricular pressure, which affects the vomiting centre of the medulla. It is most frequent when internal hydrocephalus is present.

Papilloedema (optic neuritis) is a state of venous congestion of the optic disc and retina. It is due, in all probability, to compression of the central vein of the retina as it leaves the optic nerve and passes across the subarachnoid space of the optic sheath. It is most obvious with tumours of the temporal lobe, the cerebellum and the fourth ventricle, and may be absent in subcortical cerebral tumours. The optic cup of the retina, normally depressed below the surface, fills up with oedema and may even project above the general retinal surface. The oedema spreads to the retina around it, the veins become greatly engorged, hæmorrhages may occur, and eventually secondary optic atrophy develops. Vision may remain unimpaired for a long time, but eventually there may be total blindness.

Giddiness may be a symptom of general increase in pressure or it may result from a direct effect of a tumour upon the apparatus of equilibration. It is seen most often with tumours of the acoustic nerve, the cerebellum and the pons.

Hypopituitarism is a secondary effect of an increase of intracranial pressure, and is especially common when the tumour has given rise to a state of internal hydrocephalus. The floor of the third ventricle dilates, exerts pressure upon the base of the skull, and leads to erosion of the clinoid processes and flattening of the pituitary fossa. Either from direct pressure upon the gland itself, or from obstruction to the flow of its secretion into the cerebrospinal fluid, there results a condition of hypopituitarism, with obesity, polyuria, increased sugar tolerance and sexual infantilism. The effect of intracranial tumours upon the pituitary may be demonstrated in radiograms, for erosion of the clinoid processes and enlargement of the pituitary fossa are well recognized radiographic signs of increased intracranial tension.

Affections of the cranial nerves may result from hydrocephalus. They are believed to be due to stretching of the nerves from downward displacement of the brain. The abducent nerve is involved most commonly, occasionally the trigeminal and rarely the oculomotor and facial. It is important to recognize that these disturbances are merely evidence of intracranial hypertension. They are of no value in the localization of the tumour.

DISEASES OF THE PITUITARY GLAND

It is a cause of wonder that so small an organ as the pituitary gland should play so important a part in the growth of the body and its metabolism. The gland is connected by the infundibulum to the tuber cinereum of the floor of the third ventricle. It is little larger than a pea, yet it exercises, through its internal secretions, a profound influence on growth, sexual functions, metabolism, etc.

It consists of four parts—*anterior*, *intermediate*, *tuberal*, and *nervous*—which differ from one another in derivation, in structure, and probably in function. The *pars anterior* is usually spoken of as the *anterior lobe*, and the *pars intermedia* and *pars nervosa* together as the *posterior lobe*. Between the two lobes there is a cleft-like space, which contains glairy fluid. The *pars anterior* and the *pars intermedia* are ectodermal in origin, and arise from a tubular protrusion of the oral epithelium. The *pars nervosa* also is of ectodermal origin, but is derived from the neural ectoderm, and arises as a downgrowth from the floor of the third ventricle. The *pars tuberalis* is formed from a separate outgrowth of the oral ectoderm, and in some animals it remains separate from the rest of the gland.

Histological Structure of the Pituitary Gland

The *pars anterior* is composed of two distinct kinds of cells—clear and granular. The clear cells are known as chromophobe cells, and the granular as chromophil cells. There are two types of granular cells—basophil and eosinophil; both are derived from chromophobe (mother) cells, and by special staining methods transitional types of each can be recognized. Normally the chromophobes constitute 52%, the eosinophil 37%, and the basophil 11% of the cells in the *pars anterior*. The basophil cells are increased in number following castration and after thyroidectomy.

The *pars intermedia* (poorly developed in man) is a thin strip of tissue composed of clear non-granular cells, amongst which there are vesicles filled with colloid. In places its cells extend into the *pars nervosa* and undergo degeneration to form hyaline or granular colloid material. These "colloid bodies" pass upwards through the *pars nervosa* and are eventually set free in the cerebrospinal fluid of the third ventricle. The colloid is therefore regarded as the active secretion of the *pars intermedia* and is probably derived from the basophil cells of the *anterior lobe*. Its production is greatly increased after thyroidectomy.

The *pars nervosa* is composed of neuroglia and ependymal cells. It contains no cells of a definitely neuron character. Developmentally and functionally the posterior lobe participates in the complicated processes attributed to the hypothalamus, from which it is an outgrowth.

The *pars tuberalis* is different in structure from the rest of the gland. It surrounds the infundibulum and forms a sheath for it, and the base of the brain spreads over the tuber cinereum. The *pars tuberalis* is exceedingly vascular and looks not unlike thyroid tissue; it contains areas of squamous epithelium formed, it is believed, by a process of metaplasia. In lower vertebrates this part of the gland controls melanophore activity.

The Functions of the Pituitary Gland

Knowledge of the functions of the pituitary gland, though still incomplete, has been greatly enhanced by clinical, pathological and experimental observations, and it is now proved that the gland occupies a dominating position in the endocrine system, governing directly or indirectly a surprising number of biological processes.

The anterior lobe provides at least six or more hormones. They are: (1) *gonadotropic*: which controls the development of the sex glands and the various phases of the reproductive cycle. The large quantities of the hormone found from an early stage of pregnancy in the urine and blood are the basis of the Aschheim-Zondek biological test for pregnancy. (2) *Growth*: which controls skeletal development and the time of fusion of epiphyses. (3) *Thyrotropic*: suggested by the experimental observations that hypophysectomy causes thyroid atrophy, whose effects can be controlled by replacement therapy. Excessive dosage of extracts of the pituitary leads to hyperplasia of the thyroid and a condition resembling toxic goitre. (4) *Adrenotropic*: which controls the size and activity of the suprarenal cortex. (5) *Lactogenic*: which promotes lactation at the end of pregnancy, and is believed to confer the "mother instinct" in animals. (6) *Diabetogenic and ketogenic*: suggested by the observations that (a) diabetes disappears from a depancreatized animal after hypophysectomy, and (b) that injections of anterior lobe extract will produce diabetes and ketonuria.

The posterior lobe may be removed without fatal result, and, indeed, without demonstrable effect. Very little is known of its normal physiological action, but it is believed to participate in the important metabolic functions subserved by the hypothalamic nuclei. The extract of the posterior lobe (*pituitrin*) has very active pharmacological and hormonal effects, but its mode of action in normal conditions is not yet determined. The extract contains two easily separable active principles—*pitressin* and *oxytocin*. Pitressin raises blood pressure, stimulates peristalsis, antagonizes insulin and suppresses the diuresis which follows a large intake of fluid. Oxytocin is a powerful stimulant of plain muscle and terminates pregnancy, and in this property antagonizes the hormone of the basophil cells of the anterior lobe of the pituitary.

Syndromes of Disorders of the Pituitary Gland

In the light of the known and suspected functions of the pituitary, the origin and features of its diseases are easily understandable; and it is obvious that not the pituitary entirely but other endocrine glands, especially the sex glands, share in producing the familiar clinical syndromes.

(1) **Pituitary Deficiency (Apituitarism and Hypopituitarism).** The manifestations of deficiency vary according to the extent to which activity of the gland is suppressed and the age of onset. The anterior lobe may be completely destroyed by a septic embolism (as in puerperal fever), by syphilis, cysts, tuberculosis and other causes. The result is complete apituitarism—known as *Simmonds's disease*. The condition is commonest in adult females, but it may occur in childhood. In child-

hood the deficiency is characterized by a striking premature ageing (progeria). In adults, in addition to premature ageing, there are gonadal atrophy and early and complete amenorrhœa. The viscera, particularly the intestines, undergo atrophy and the other endocrine organs are diminished in size. There is usually very marked arterial hypotension and sometimes hypoglycæmia.

Less severe grades of deficiency are much more common. They may be due to delayed development of the gland, hydrocephalus, or the destructive effects of tumours. In children the most striking changes are infantilism and adiposity. With infantilism the body is not necessarily short but is slender. The sexual organs are immature, secondary sexual characteristics fail to develop, and puberty does not occur. Obesity may be generalized, or may be localized to the pubic area (dystrophia adiposa genitalis).

In young adults the most notable changes are depression of the sex function and obesity with increase of carbohydrate tolerance. In men, there are depression of sexual activity and genital atrophy. In women, amenorrhœa is often an early manifestation, and later the genital organs involute.

(2) **Pituitary Over-activity (Hyperpituitarism).** Pituitary over-activity is most commonly due to excessive secretion of the eosinophil cells (hyperpituitarism), and much less frequently to exaggerated activity of the basophil (basophilism): there is a syndrome characteristic of each. The latter is often associated with pathological changes in the suprarenal cortex.

(a) When hyperpituitarism develops during the period of growth, gigantism occurs, in later life acromegaly.

In gigantism growth of the skeleton continues beyond the usual period of adolescence, and the epiphyses remain ununited. In addition, the sex organs often remain atrophic, and the secondary sexual characters are under-developed.

In acromegaly the most obvious changes are overgrowth of the skeleton, most definite in the skull and facial bones, and in the vertebral column and phalanges. The chief changes in the skull are increased thickness of the bones and enlargement of the natural ridges. In the face the zygomatic bones become prominent, the mandible enlarges (prognathism), and as the teeth do not enlarge coincidentally with the jaw they may be widely separated. Kyphosis in the thoracic region is the most notable change in the vertebral column. The phalanges are enlarged and exostoses may develop on them.

In prolonged hyperactivity the skin and subcutaneous tissues become thick, inelastic, and coarse. Other soft organs may be enlarged: the nose is broad, the lips thick, and the tongue hypertrophied. Internal organs also, *e.g.*, the colon, may be enlarged.

(b) In over-activity of the basophil cells arising from an adenoma, a very characteristic syndrome may develop—the pituitary basophilism of Cushing. The features of this condition resemble closely those of a tumour of the adrenal cortex (*see* p. 605), and it may be difficult to ascertain whether pituitary or adrenal gland is responsible.

However, it has been shown by both biological and colorimetric

assays of the urine that, especially in females, the androgen output per day in the case of adrenal cortical tumours is as high as 250–300 international units (normal 16 to 80 units), whereas in Cushing's syndrome the androgen output lies within the usual limits or is slightly lower than normal.

It affects women much more frequently than men. The onset is fairly abrupt with a marked increase of the subcutaneous fat of the face, neck, and trunk. The skin assumes a dusky or plethoric appearance, and purple lineæ atrophicæ may develop. Hirsuties is a striking feature. The patient suffers from backache and abdominal pains and is easily fatigued. In women amenorrhœa occurs early, in men impotence. There is commonly pronounced decalcification of the skeleton which may lead to kyphosis, and, in many instances, to fractures of the long bones. A very constant feature is vascular hypertension and a tendency to polycythæmia. The urine may contain a follicle-stimulating substance. At post-mortem, hypertrophy of the ovaries, the thyroid gland and the suprarenal cortex is commonly present.

(3) **Additional Signs of Disease of the Hypophysis.** (a) *Diabetes insipidus* is an inconstant feature; it sometimes results from the pressure of suprasellar tumours. It is now conceded that the extreme polyuria, excessive thirst and emaciation are due to involvement of the hypothalamic nuclei which control water-metabolism. The pituitary may be destroyed or removed without the occurrence of diabetes insipidus, yet even if the pituitary is not implicated, injections of pituitrin are usually effective in controlling the polyuria. Thyroidectomy may benefit intractable cases.

(b) *Adiposity*, though often a very striking feature, is an inconstant one. It is much commoner in young subjects. It is probable that the adiposity is secondary to atrophy of the sex glands and therefore resembles the obesity that may follow castration.

TUMOURS OF THE PITUITARY GLAND

Tumours are the commonest diseases of the pituitary gland and account for about 15% of all intracranial tumours. They are classified according to the tissue from which they arise, and according to their position relative to the gland itself. A simple adenoma is by far the commonest. It arises in the anterior lobe, and while small is entirely within the sella turcica—i.e., intrasellar. It is named chromophobe, chromophil, basophil, or transitional, according to the pattern of cell which predominates. An adeno-carcinoma may occur but is exceedingly rare. The other common tumours arise in relation to the pars tuberalis and are of epidermoid character (cranio-pharyngioma), and, in exceptional cases, from the interglandular cleft in the form of a distension cyst of an embryonic vestige (Rathke's embryonic invagination of the stomodeum). The epidermoid tumours, from their anatomical position and their common (though not invariable) cystic character, are known as *suprasellar cysts*.

Primary tumours in the *pars nervosa* are unknown, but it is frequently the seat of metastases.

Pituitary Adenoma

The adenoma is a small tumour, usually of pale yellow colour, but may become a dark maroon from extravasated blood. It is soft or firm, according to the rate of growth and, like other adenomata, may undergo cystic degeneration.

The **chromophobe adenoma** is much the commonest type and occurs between the ages of twenty and forty years. It is composed of groups of clear, non-granular cells of an embryonic type (see Fig. 126); they may be arranged in alveoli,

flat sheets, or in papillary formation. The tumour furnishes no endocrine secretion, and its pathological effects are due to the pressure it exerts on the hypophysis. The constitutional effect of such a tumour is therefore hypopituitarism, in which there may be inhibition of both growth and maturation.

The **chromophil or eosinophilic adenoma** is usually of smaller size and is composed of richly granular cells that resemble the normal epithelium of the anterior lobe (see Fig. 127). Chromophobe cells also are almost always present but they are not of an embryonic type. The tumour, although it impinges upon and destroys the hypophysis, produces an endocrine secretion,



FIG. 126. Chromophobe adenoma of the hypophysis. The cells are large, non-granular, and uniform in shape and size.

(Laboratory of Royal College of Physicians of Edinburgh.)

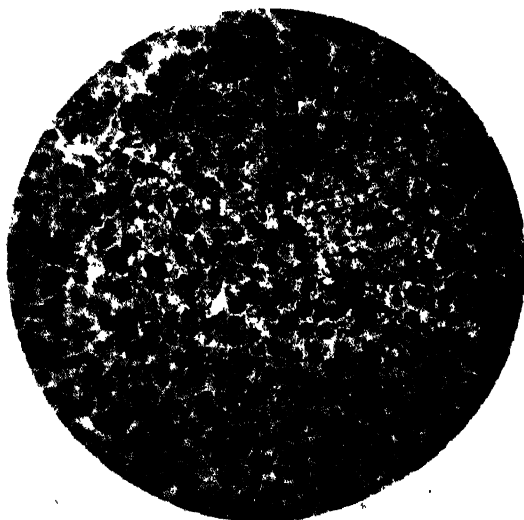


FIG. 127. Chromophil adenoma of the hypophysis from a case of acromegaly. The sinusoidal character of the normal anterior lobe is lost. The cells are large and irregular, and the majority are acidophil.

(Laboratory of Royal College of Physicians of Edinburgh.)

and it is constantly associated with the syndrome hyperpituitarism, usually evidenced by marked sex dysfunction. As it is most common after the age of twenty years, acromegaly is the usual result.

The transitional or mixed adenoma is composed of chromophobe cells with eosinophilic cells in varying numbers. It is usually larger than a pure eosinophilic adenoma. It destroys the gland, but on account of its content of eosinophil cells it maintains the secretion, with the result that there may be blending of the features of hypo- and hyper-pituitarism. The common age of occurrence is twenty to forty years.

The basophil adenoma is the rarest type of pituitary tumour. It is

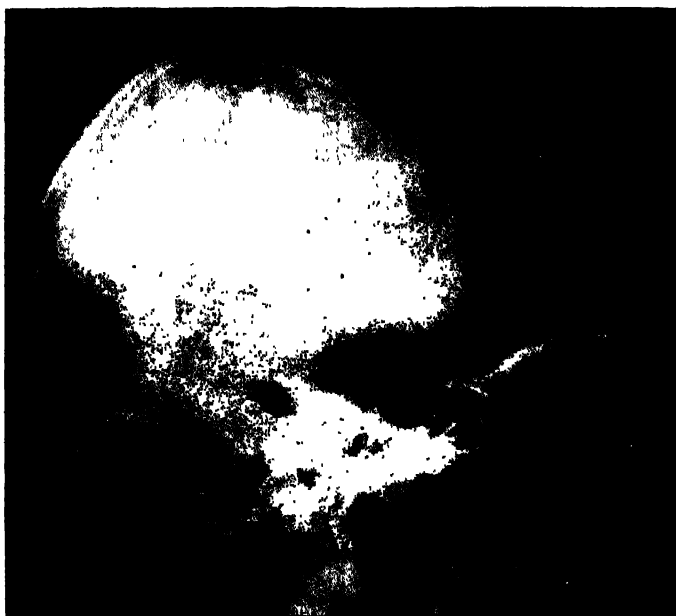


FIG. 128. Pituitary adenoma. Note the expansion of the sella turcica.

(By courtesy of Dr. Scott Park.)

usually small, seldom more than 2 cm. in its greatest diameter, and therefore pressure effects are lacking. Microscopically, it resembles an eosinophil adenoma, but with special strains the cells are found to contain basophil granules. The tumour may be associated with Cushing's syndrome or "basophilism" (*see* p. 291), but the relationship is not a constant one, and sometimes a basophiladenoma causes no symptoms. When present it has been observed that the basophil cells of the gland show degranulation of their cytoplasm but the cells of the tumour are unaltered.

Adenocarcinoma is exceedingly rare. It is composed of cells of chromophobe type arranged in irregular groups or solid cords; it is very vascular, and cystic degeneration frequently occurs in it. The tumour destroys the hypophysis, invades the surrounding tissues and

nerves, and causes paralysis. Metastases may occur in the liver and elsewhere. Most cases have occurred after the age of forty-five years.

Cysts of the Interglandular Cleft (or Rathke's Pouch). In rare instances a cyst may develop in connexion with the epithelial lining of the interglandular cleft. It is lined with a single layer of columnar epithelium which may be ciliated. The cyst is intraglandular and intrasellar in origin and therefore destroys the gland, and by extension may produce local pressure effects.

The Local Effects of Adenoma of the Pituitary

Growth of an adenoma is much restricted by the bony boundaries of the sella turcica and its dural roof—the diaphragma sellæ. It is therefore not surprising that the gland is gradually compressed and destroyed by the expanding tumour. In its attempt to secure accommodation the tumour expands the bony walls of the sella turcica, which in a radiogram shows a characteristic globular distension (*see* Fig. 128). Finally, the bone may be eroded so that the tumour projects into the sphenoidal air sinus and may lead to epistaxis and pharyngeal discharge. Lateral expansion of the tumour compresses or displaces the cavernous venous sinus and may paralyse the oculomotor or the abducent nerve; occasionally the ophthalmic and maxillary divisions of the trigeminal nerve are affected. Upward extension causes stretching and occasionally rupture of the diaphragma sellæ, and when that happens the tumour may impinge on the optic chiasma. As a rule it is the antero-inferior part of the chiasma that is subjected to pressure, and primary optic atrophy with blindness occurs. The characteristic change in the visual field is bitemporal hemianopia manifest first in its upper lateral quadrant. At a later stage the hypothalamic region and the uncinate area of the hippocampal gyrus may be indented by upward and lateral extension of the tumour, and somnolence and other effects referable to pressure on these structures are produced. Only when the third ventricle is compressed or the aqueduct obstructed do signs of increased intracranial tension become evident.

Suprasellar Epidermoid Tumours (Craniopharyngioma)

The common suprasellar tumour is of epidermoid character. It is commonest in youth and over 75% occur before the age of forty years. The tumour arises above the diaphragma sellæ in relation to the pars tuberalis from islets of squamous cells within that structure. Whether the cells are embryonic rests or developed by metaplasia has not been fully settled.

The tumour is usually cystic but may be solid. At the base of the cyst there is generally a warty projection. Histologically, it is of epidermoid structure, most often well differentiated with keratinization and cell rests, sometimes of basal cell type, and rarely of enamel cell type (adamantinoma). Fatty substances are frequently present in the stroma and their calcification (which is present in 85%), affords a significant sign in radiographic interpretation.

A suprasellar tumour usually begins just beneath the aperture of

the diaphragma sellæ, and, at this point, lies within the cisterna chiasmatis. As growth proceeds it bulges upwards rather than downwards; on an average it has the dimensions of a walnut but may be very much larger.

A suprasellar cyst has no endocrine secretory faculty and its effects are referable chiefly to pressure. At an early stage it impinges on the hypothalamus, and therefore polyuria is an early symptom. Later there may be compression of the optic chiasma and the pituitary, and the combined effects may result in Fröhlich's syndrome and diabetes insipidus. The dorsum sellæ and the clinoid processes may be eroded as a result of pressure and, in a radiogram, such changes may afford valuable evidence in diagnosis.

Surgical Aspects of Pituitary Tumours

Suprasellar tumours bulge into the subarachnoid space and impinge on the mid-brain, the optic nerves or chiasma. The tumour may be very firmly adherent to the margins of the sella turcica. Removal of a suprasellar tumour is only possible by an intracranial operation, and when it is situated laterally or far back access may only be obtained by sacrifice of one of the optic nerves. In operating care must be exercised to avoid laceration of the floor of the third ventricle, an accident which usually proves fatal.

In pituitary adenoma operation is designed to relieve headache and to prevent or relieve blindness. In a few cases progression of endocrine disturbances may be prevented. For preference, the tumour is approached from within the skull and an attempt is made to remove the greater part of it. When an adenoma is of slow growth and has not developed an intracranial extension, and especially, as in acromegaly, when the subject is in poor condition, it is most easily dealt with by the transphenoidal route, which permits of a partial removal of the tumour and affords a decompression of the expanded sella turcica. In rare instances tumours bulge into the third ventricle and are only accessible *viâ* the frontal lobe and lateral ventricle.

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CHAPTER XIV

DISEASES OF THE SPINE AND SPINAL CORD

SPINA BIFIDA (*Rachischisis*)

THE spinal cord, like the brain, is derived from the ectoderm of the dorsal surface of the embryo. A strip of ectoderm, the *neural plate*, becomes raised above the general surface, and then in succession hollowed out as a groove, depressed below the surface, and folded sagittally to form a tube. This *neural tube* later becomes further depressed, and then separated from the surface ectoderm by an intrusion of mesoderm growing in from either side. The processes of tubulation and of separation from the skin surface are completed last in the lumbar region, and it is here that developmental anomalies are most common.

There are many types of spina bifida, but some of these being incompatible with life are of interest only to the teratologist, and for practical purposes a simple classification will suffice.

(1) **Complete Rachischisis.** This is a gross abnormality resulting from failure of development of the whole length of the column. The cord fails entirely to separate from the superficial ectoderm and remains exposed to the surface in a shallow gutter in the midline of the back. The condition is incompatible with life.

(2) **Partial Rachischisis.** This type includes all the less extensive defects that involve only a limited portion of the cord. The defect is most often situated in the thoracico-lumbar or lumbo-sacral region, rarely in the cervical region. It may be a severe lesion, incompatible with life, or may be so small as only to be discovered on careful examination. Three principal varieties and two rare ones are recognized.

(a) **Myelomeningocele.** This is a gross deformity, and often the child is still-born or dies within a few days of birth. There is a defect of the vertebral laminæ and spines and in the soft tissues over a limited area, usually in the thoracico-lumbar region, and the cord in this part of its course lies in its primitive position close to the skin surface. Three or more of the vertebræ are usually affected. The spinous processes are absent, the laminæ are represented merely by short stump-like projections, and the vertebral canal consequently forms a shallow trough with no posterior wall. The cord, which at higher levels lies normally in the vertebral canal, at the position of the defect comes to lie more superficially. In some cases it lies completely exposed in the floor of a shallow gutter, and it then has a raw red appearance as of congested granulation tissue. This variety is sometimes known as a *myelocele*.

In other cases the cord is raised on the surface of a cystic swelling, which is sometimes of large size. Since this is the type most often seen

surgically it requires a fuller description. The protrusion is situated in the midline, where it forms a somewhat oval and irregularly lobulated sessile mass, in the summit of which lies the abnormally placed cord. The cord, retaining the shape of the embryonic neural plate, forms a flat, plaque-like strip of tissue which is evident as an oval area, bluish or congested—the *area medullo-vasculosa*. In some cases this area is covered with a thin layer of epidermis, with which it is closely fused. In other areas, epidermis is lacking, and the nerve tissue is covered only by soft red granulations. Near the upper end of this area there is sometimes a small orifice, which represents the termination of the central canal of the cord. For the first few days of life a little cerebrospinal fluid may escape here, but the orifice is soon closed by oedema. Occasionally a similar orifice is present at the caudal end.

Around the *area medullo-vasculosa* and continuous with it lies the

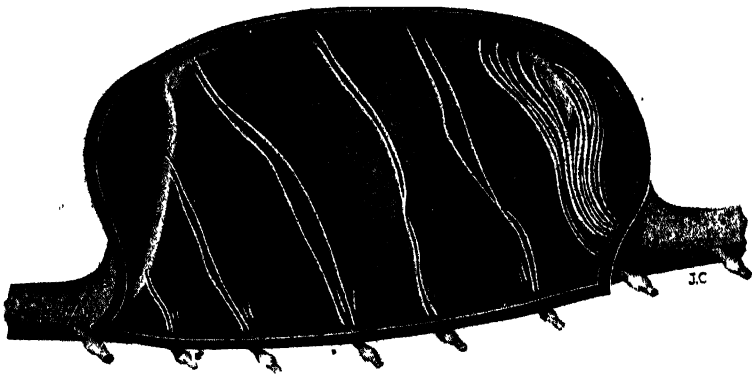


FIG. 129. Myelomeningocele exposed by longitudinal section. The malformed spinal cord is seen at the summit of the sac. On the right, the filaments of the cauda equina pass deeply to gain the vertebral canal. Note the expanded ligamentum denticulatum.

(By courtesy of Professor Sir J. Fraser.)

zona epithelio-serosa, which represents the area of fusion of the skin with the membranes lining the sac, the dura mater and arachnoid. It is thin and often of bluish colour, and laterally, where it gradually merges with the surrounding skin, there are often small telangiectases and epithelial overgrowths.

The sac may be unilocular or multilocular. It contains cerebrospinal fluid, and on its deep aspect it communicates with the spinal subarachnoid space, of which it is merely a greatly enlarged portion. The cavity is traversed by pairs of nerve roots, which arise in the abnormally placed portion of the cord and proceed deeply to the vertebral canal to gain exit through the intervertebral foramina. Each nerve, as it traverses the sac, is supported by a fold of arachnoid, which attaches it, as by a mesentery, to the sac wall. The sac is also partly divided into compartments by the ligamenta denticulata, which form broad sheets that pass backwards on either side of the midline. Sometimes at the lower end of the sac the cord is reconstituted and re-enters the spinal

canal. More often, however, the termination of the cord lies in the sac, and the fibres of the cauda equina pass deeply to gain the canal and their proper exits.

A myelomeningocele is often accompanied by other defects. There are usually deformities of the lower limbs or paralyses resulting from failure in the development of the cord, and there may be such unrelated lesions as hypospadias, cleft palate or hare-lip. Hydrocephalus is often present. The treatment is very unsatisfactory, for though it is technically possible to replace the cord in its proper position this does not rectify the associated paralysis. Moreover, the operation itself is a severe one for a young infant, and, since the surface of the exposed cord cannot be sterilized, meningitis often supervenes.

(b) **Meningocele.** This is a rather uncommon deformity. It may be likened to a herniation of the meninges of the cord (arachnoid and dura mater) through a gap in the bones and soft parts. The cord itself is unaffected and lies in its bony canal, and the nerve roots usually lie in their normal position. The spinous processes of the affected vertebræ, usually two or three in number, are absent, and the laminæ are represented merely by short projections on the posterior surfaces of the transverse processes. The membranes projecting through this gap form a cyst-like swelling under the skin in the midline of the back. Typically, the swelling is covered by thin skin, which may be scarred, in places. It contains cerebrospinal fluid, and is translucent. Usually there is no associated paralytic lesion, but hydrocephalus or other congenital deformities may be present.

(c) **Spina Bifida Occulta.** Here the obvious defect is minimal. The cord is completely formed and lies in its bony canal, and the membranes are intact, but the spines and laminæ of one or more vertebræ are abnormal. Sometimes the spines are absent and the laminæ defective, and there is a palpable defect in the midline of the back. In other cases the spines are bifid. The skin surface may be of normal appearance but often is dimpled, and there may be dilated vessels, a tuft of hair, or small fatty or fibrous tumours.

The defect may give rise to no symptoms and remain unrecognized, except perhaps on chance clinical or radiographic examination, or it may lead to paralytic deformities of the lower limbs, such as pes cavus or other forms of talipes. These deformities usually develop during adolescence and are often bilateral.

The paralytic effects are attributable to the presence of the *membrana reuniens*, a tough fibrous band passing from the deep aspect of the skin to the membranes of the cord. In early life the *membrana reuniens* remains lax and causes no symptoms, but during adolescence or early adult life it fails to keep pace with the growth of the rest of the body and with the slight upward movement of the cord in its canal, so that traction may be imposed upon it. The dura mater, to which the membrane is attached, is drawn superficially and slings the cord in that direction. Thus the pull of the *membrana reuniens* is transmitted to the anterior part of the cord, which is compressed, and consequently the paralytic phenomena are almost entirely motor. Trophic changes in the skin, especially of the feet, are common.

(d) **Syringocele** (Syringomyelocoele). In this condition the cyst-like swelling represents a greatly dilated portion of the central canal of the cord, and the cavity is consequently lined by modified, compressed nervous tissue. It is a very rare type of anomaly.

(e) **Anterior Rachischisis**. This is an exceedingly rare form of rachischisis in which the sac protrudes anteriorly, through a defect in the vertebral bodies. It may form a protrusion in the abdomen or pelvis and be mistaken for a tumour or cyst. It is rarely compatible with life and is not amenable to treatment.

SPONDYLITIS DEFORMANS

This title includes a variety of diseases of the spinal column characterized by varying degrees of stiffness and pains in the back. In some cases the disease affects young adults, causing much pain and progressing to complete rigidity of the back with marked disability; in others it affects elderly persons, giving rise to the rounded shoulders, bent back and stiffness so common in old age.

Sometimes a cause is to be found, *e.g.*, a dental focus of infection or a gonococcal prostatitis; more often the origin of the disease can only be ascribed to chronic degenerative changes or to repeated trauma.

Two main types may be recognized, the osteo-arthritic and the ankylosing types.

Osteo-arthritis of the Spine.

This disease may occur alone or in association with disease of other joints, and it is generally regarded merely as a special type of osteo-arthritis with certain special features related to the special anatomy of the spine. The disease commonly occurs in elderly people. The articulations are affected primarily; later the ligaments and the intervertebral fibro-cartilages may be involved. In some cases the disease affects multiple intervertebral joints and also the costo-vertebral joints; in others, and more commonly it is localized to one part of the column, particularly the lumbar segment.



FIG. 130. Spondylitis deformans. The vertebral column is ankylosed in a position of kyphosis. There are osteo-arthritic changes in the intervertebral and costo-vertebral joints, and the vertebral bodies are united by plaques of new bone.

(Museum of Royal College of Surgeons of Edinburgh.)

The articular cartilages and bone are eroded and chondro-osteophytes develop at the margins. Often also exostoses arise from contiguous margins of the vertebral bodies and project laterally as sharp spurs, or bridge the gaps between adjacent bodies. The intervertebral fibro-cartilages undergo gradual absorption and become thinned, as though from pressure, while not infrequently the vertebral bodies become wedge-shaped. Very rarely the ligaments of the vertebral column become ossified.

Arthritis of the spine causes stiffness of the back and may cause "rheumatic" pains, which are accentuated by climatic changes or by sudden twisting movements. Often the pain is referred to the distribution of sensory nerves, particularly the sciatic nerve. These effects are usually ascribed to pressure of osteophytes on the nerves as they emerge from the intervertebral foramina, hence the special tendency to involvement of the fourth and fifth lumbar roots of the sciatic, which are large nerves almost filling the bony canals.

Spondylitis Ankylopoietica. This very disabling disease generally occurs in young adults, especially in males, and gives rise to severe persistent pain and marked rigidity of the spinal column. It may progress rapidly until the whole spine—and the sacro-iliac joints and sometimes also the hip joints—are completely ankylosed, or it may take a chronic course with remissions lasting many months or years.

The first signs are often seen in relation to the sacro-iliac joints; later all the intervertebral and costo-vertebral joints may be involved. The joint cartilages are eroded and the bone adjacent undergoes rarefaction, and this is later followed by osseous ankylosis, so much so that eventually in radiographs no trace of the joint outline remains. The intervertebral cartilages also are thinned, while exostoses projecting laterally bridge the gaps between contiguous vertebrae, giving a radiographic appearance often compared to a bamboo stick.

AFFECTIONS OF THE INTERVERTEBRAL DISCS

The investigations of Schmorl have focussed attention upon certain affections of the intervertebral discs which had not previously been recognized. A disc consists of three portions. There is a peripheral ring, the *annulus fibrosus*, composed of tough fibro-cartilage firmly attached to the vertebral bodies and to the anterior and posterior longitudinal ligaments. On the two surfaces of the disc are thin plates of hyaline cartilage, which are set directly in contact with the spongy bone of the vertebral bodies. These plates serve a double function, acting as epiphysal cartilages for the vertebral bodies as well as retaining capsules for the nucleus pulposus.

The *nucleus pulposus*, the third element of the intervertebral disc, is contained within the annulus and between the cartilage plates. It forms a semi-gelatinous mass consisting of loose fibrous tissue containing scanty cartilage cells and large multinucleated cells (rudiments of the notochord) set in a gelatinous matrix. The nucleus is confined within the disc under tension, imparting an elastic quality to it, and thus giving a high degree of resilience to the vertebral column as a whole.

As a result of trauma or degenerative changes, the nucleus pulposus may prolapse through a fissure in one of the cartilage plates or in the annulus fibrosus. Such a protrusion of the nucleus is a common cause of pain in the back, sciatica, and other pressure effects.

If the protrusion takes place through one of the cartilage plates of the disc, the nuclear substance prolapses into the spongy bone of the vertebral body, and there sets up reactive and degenerative changes, resulting in a cavity within the bone surrounded by osteosclerosis. These changes in the bone, combined with the loss of elasticity which results from escape of the nuclear substance, may be a cause of pain and stiffness of the spine and may predispose to spondylitis deformans.

If the protrusion takes place through the annulus fibrosus, the nuclear substance generally prolapses towards the spinal canal and projects within the canal in the form of a button-like prominence to one or both sides of the posterior longitudinal ligament. If such a protrusion is situated in the thoracic part of the spine it may exert pressure on the cord and give rise to mild paresis, generally of spastic type and sometimes accompanied by sensory changes.

The commonest site for prolapse of the nucleus is at the fourth and fifth lumbar disc. For this reason the commonest clinical manifestation is pain referred to the sciatic nerve. Clinically the condition is identical with other types of sciatica and is characterized by pain in the sciatic distribution exaggerated when the nerve is stretched, by tenderness along the nerve trunk and by diminution or absence of the ankle-jerk. In some cases there are additional features such as flattening and rigidity of the lumbar spine, lumbar scoliosis, and paræsthesia with slight muscle wasting in the leg.

The nuclear prolapse responsible for sciatica is usually situated at the lumbo-sacral junction or at the last lumbar intervertebral disc. In some cases operation shows the affected nerve root stretched over the prolapse, which has the appearance of a small glistening white swelling lateral to the posterior longitudinal ligament. In other cases there is no true prolapse or herniation of the nuclear substance, but a diffuse bulging of the circumference of the disc.

TUMOURS OF THE SPINAL CORD

The spinal cord, like the brain, may be affected by tumours within its substance or by tumours arising from any of the structures around it. It is customary to classify the tumours in three groups, according to their relation to the cord and its membranes.

(1) **Extradural tumours** include all those that arise in the bones, cartilages and soft parts of the vertebral column, and also those rare growths that invade the spinal canal from without.

In the bones of the vertebral column the commonest tumours are secondary deposits of carcinoma, from tumours of the breast, prostate, thyroid gland, kidney, or other organs. Less often the tumour is primary in the vertebræ, for instance, osteoma, chondroma, hæmangioma and sarcoma. The vertebræ are liable to be involved also in

myelomatosis. All these types of growth occur more commonly in the vertebral bodies than in the laminae or processes.

A chondroma occasionally arises from the intervertebral fibro-cartilages. A fibroma, lipoma, sarcoma, or hæmangioma may arise from the extradural connective tissue, a neurofibroma from the extradural portions of the spinal nerves, a chordoma from rudiments of the notochord. A tumour that originates in the extradural space and spreads outwards through an intervertebral foramen, and one that invades the canal from without, tends to assume an hour-glass shape in virtue of the spaces it traverses.

(2) **Intramedullary tumours** arise in the tissues of the cord itself. They are of the nature of gliomata, and in general have the characteristics of similar tumours in the brain. They tend to spread in the nerve tissue diffusely, without encapsulation, but as a rule do not spread to its membranes. Extension of the tumour is sometimes rapid, and occasionally the tumour infiltrates several centimetres of the cord, or even its whole length, which becomes swollen and of soft fleshy appearance. The symptoms and signs of intramedullary tumours are usually somewhat indefinite, and as the progress of the disease is rapid such tumours are seldom suitable for operation.

(8) **Intradural extramedullary tumours** are generally derived either from the arachnoid mater or from the intradural parts of the spinal nerve roots. They have the character either of meningioma or of neurofibroma. Tumours of this group are commoner than intramedullary and extradural tumours (excepting metastatic tumours), and are also of much greater surgical importance, for they are usually non-malignant, they give rise to characteristic neurological features which render accurate diagnosis possible, and they can be removed, often with complete restoration of function.

The majority of tumours in this class conform to one general type and are of slow growth and non-malignant. A tumour of this type is small, rarely exceeding 5 cm. in length, and usually oval or elongated in the long axis of the cord. It is encapsuled by tissue derived from the arachnoid membrane, and lies on the inner aspect of the dura mater, to which it is often firmly attached. The tumour is usually related to one of the posterior (sensory) nerve roots, and for this reason it is situated, in 75% of cases, on the postero-lateral aspect of the cord; less commonly it appears to arise from an anterior root or from the meninges in front of the cord. In the majority of cases the thoracic portion of the cord is affected, but no portion is exempt.

Usually the tumour is of firm, fibrous consistence and has a somewhat scanty blood supply derived from a single small arterial twig. In other cases the vascularity is greater. Often the tumour is partially calcified, and is then sometimes known as a *psammoma*.

Microscopically, it resembles an endothelioma. Flattened endothelial cells, or spindle-shaped cells of fibroblastic type, are set in a well-formed fibrillar stroma. Often the cells exhibit whorl-formation. There are usually areas of hyaline degeneration and of calcification, and there is often some lymphocytic infiltration.

Effects of the Tumour. The effects of tumours of the intradural extra-

medullary group are usually characteristic. At first only the related nerve root is affected. Later the cord is displaced and compressed, though never invaded. Pressure upon the cord for a long time causes only irritation and oedema. Later the nerve cells and fibres undergo pressure necrosis (sometimes aggravated by thrombosis of vessels), and irreparable damage is done. The meninges around the tumour, though not invaded, are curiously thickened, as though inflamed, and are often unduly vascular.

The pathological changes are reflected in the clinical features. At first there is evidence of interference with a single posterior nerve root. "Root pain" is referred to the area of distribution of the nerve, and there may be paræsthesiæ, with sensations of tingling, numbness, heat and cold. Complete block of nerve conduction may lead to areas of anæsthesia, but this is often masked by the overlapping distribution of adjacent sensory nerves.

At a later stage the tumour presses upon and indents the cord, affecting first the nearest cells and tracts, later half the cord and eventually its whole thickness. The effect of pressure is to damage the grey matter at the level of the tumour, and to interrupt impulses passing along the fibres in the white matter. Thus a tumour pressing on the lower cervical cord may give rise to a lower neuron paralysis of the arm on the corresponding side, and an upper neuron paralysis of the lower parts of the body. When only half the cord is affected the Brown-Séquard syndrome may result, in which there is muscular paralysis with loss of deep sensation on one side and paralysis of the sensations of pain, heat and touch on the other. Eventually the tumour compresses the entire cord and complete paraplegia develops.

When the tumour grows sufficiently to press upon and stretch the surrounding membranes, it may give rise to pain locally over the affected portion of the spine, and this area becomes tender on direct pressure.



FIG. 131. Spinal meningioma. The tumour lies in close relation to the posterior nerve roots of the cervical enlargement of the cord. The tumour is of small size and encapsuled. It has compressed, but not invaded the cord.

(Department of Clinical Surgery, University of Edinburgh.)

In those regions where the cord occupies most of the available space, as at the cervical and lumbar enlargements, a small tumour will soon cause pressure effects, and moreover an affection of the specialized tissues supplied by these regions, as of the muscles of the hand, will be noticed early. In other regions, and especially in the region of the conus and cauda equina, where the vertebral canal is spacious, a tumour may attain large size, yet cause few symptoms.

In most parts of the cord the effects of a tumour are for a long time limited to one or two segments. In the lumbar, sacral, and coccygeal regions, however, where the segments are crowded together, the effects are more widespread.

In the upper cervical region a tumour may affect the lower cranial nerves, and cause difficulty in swallowing or in articulation, or it may compress the origin of the phrenic nerve and embarrass respiration. In the cervical and upper thoracic region a tumour may interrupt fibres going to the cervical sympathetic chain and lead to dilatation of the corresponding pupil and enophthalmos.

Effects of Obstruction of the Spinal Canal. A spinal tumour or any other lesion (tuberculous, inflammatory, etc.) that obstructs the free flow of fluid down the spinal canal produces characteristic effects. These effects, which may be recognized by hydrostatic, chemical, and radiological observations, are often of assistance in confirming the diagnosis and in localizing the exact site of the obstructive lesion.

(1) *Hydrostatic Tests.* If the tumour is situated at the usual level for lumbar puncture, attempts at aspiration at this site will fail to obtain fluid. Usually the tumour is situated above the level of lumbar puncture, and then the pressure of fluid is usually low, though occasionally (perhaps from some valvular action) it is raised. Alterations of pressure may be demonstrated most clearly by the so-called Queckenstedt test, which depends upon the fact that temporary compression of the jugular veins, by increasing the intracranial tension, normally causes an immediate spurt of fluid from the lumbar puncture needle; any obstructive lesion in the spinal canal tends to prevent this, and if the obstruction is sufficiently complete the rise of pressure is diminished or absent. A modification of the same test is that of Ayer, which consists in performing simultaneous lumbar and cisternal puncture. When the jugular veins are compressed the pressure at the two needles may be compared, and any delay in transmission of the wave of pressure may be recorded.

(2) *Chemical Tests.* Chemical examination of the fluid obtained by lumbar puncture is often of value. Stagnation of fluid below the tumour combined with transudation from dilated meningeal veins causes an increase in the protein content and a yellow discoloration. The protein of cerebrospinal fluid normally amounts to less than 40 mgm. %, and any increase above 50 mgm. % without corresponding increase in cells may be regarded as abnormal. The combination of massive coagulation of the fluid, and a yellow discoloration (xanthochromia) constitutes Froin's syndrome. When fully developed, it is strong evidence of obstruction within the spinal canal, though not necessarily by a tumour.

(3) *Radiological Tests.* Radiological examination is sometimes

necessary for the exact localization of the tumour, though often this can be made from simple neurological examination. The examination is assisted by the intrathecal injection of lipiodol, which is opaque to X-rays. Lipiodol of light specific gravity may be introduced through a lumbar puncture needle, or heavy lipiodol may be injected into the cistern. As the oil ascends or descends the canal, part or all of it may be arrested at the site of obstruction.

ANTERIOR POLIOMYELITIS (Infantile Paralysis)

In virtue of its paralytic sequelæ, poliomyelitis is the commonest of all causes of crippling in childhood, and constitutes a problem of vast importance, both surgically and epidemiologically.

At its inception it has the characters of a general infection. The main incidence falls upon the central nervous system, but changes occur also in other parts of the body, particularly in lymphoid tissues and parenchymatous organs, which show various degrees of cloudy swelling and degeneration.

There is ample evidence that the disease is infective, and the causal agent a filter-passing virus, which probably gains access to the body through the mucous membrane of the upper air passages. It is inferred that the virus reaches the central nervous system directly, along the fibres of the olfactory nerve, but a blood-borne infection is more likely. Flexner and Noguchi have shown that such a virus can be isolated from the spinal cord of patients, and that when injected into monkeys reproduces the characteristic lesions. Most cases of poliomyelitis occur sporadically, but not infrequently there are minor epidemics, which are especially apt to occur during the summer and autumn. Children may be affected at any age, but the disease is rare in infancy and the great majority of cases occur between the third and fifth years. There is a well-marked natural immunity to the disease, and it has been estimated that only about 2% of the population are susceptible. A single attack gives lasting immunity, and for many years afterwards the serum contains anti-bodies. The serum of a convalescent patient may be used in the treatment of the acute phase.

The pathological changes in the central nervous system are most obvious in the anterior horns of the spinal cord at the level of the lumbar enlargement, and consequently the most drastic and most lasting effect is motor paralysis of the lower extremities. In the acute phase of the disease, however, the posterior columns are also affected, and this may give rise to pain and tenderness in muscles and joints which may obscure its recognition. At first the affection is often widespread throughout the cord and even the brain, and may lead to a fatal result from implication of vital centres.

At an early stage the signs of inflammation appear both in the meninges and in the substance of the cord itself. Microscopically, the striking feature is the presence of lymphocyte collections, especially in the perivascular spaces in the anterior horns of grey matter, and along with this there is extensive oedema as well as congestion and petechial hæmorrhages. These changes are not uniformly distributed but

are patchy, and consequently some nerve cells are affected, whilst adjoining ones escape. The nerve cells may be affected directly by the toxins of the virus, but more probably they succumb to the mere mechanical effects of œdema and ischæmia. After the acute phase a focal sclerosis of the neuroglia may damage the nerve cells still further.

The cerebrospinal fluid becomes altered early in the disease, and its examination has a certain diagnostic value. In the first week the characteristic feature is an excess of lymphocytes, and later there is an increased globulin content. Fehling's solution is usually reduced. As a rule the fluid is clear and colourless and does not show any great increase of pressure.

The paralytic lesions are almost invariably of lower motor neuron type; the muscles are therefore flaccid and tend to waste, and their reflexes diminish. At first the paralyzes may be widespread, but since the nerve cells are not destroyed, merely compressed, a remarkable amount of restitution of function usually occurs. Almost always, however, some residual lesion remains, and subsequently leads to deformity. Generally this residual paralysis is restricted to one lower extremity, and very often merely to one group of muscles, such as the peroneal or anterior tibial or quadriceps group. The usual deformity is therefore some form of talipes with drop-foot and instability of the ankle. Sometimes the quadriceps femoris group of muscles is affected, and the knee thus rendered unstable. Paralysis of the abductors at the hip is not uncommon; it is very disabling as it prejudices the maintenance of the erect posture. In addition to the muscle atrophy there are trophic disturbances, and the growth of the limb is impaired. Less often an upper extremity is involved, and then the muscles around the shoulder are especially liable to atrophy. In other cases both legs or three or four limbs and the trunk are affected, but even then the paralysis in any one limb is rarely complete, and some few fibres in certain muscle groups remain active. This capricious distribution has important practical results, for the healthy muscles, being unopposed, contract, and often draw the limb into positions of disabling deformity.

TUMOURS OF THE NOTOCHORD: CHORDOMA

The notochord, the primitive entodermal axis around which develops the mesoderm of the vertebral column, normally disappears almost completely in early fetal life. Occasionally a portion of its cephalad extremity persists at the base of the skull, and in infancy traces may be found as the nucleus pulposus in any intervertebral disc and in the region of the coccyx. The persistent rudiment at the base of the skull is said to be present in about 1% of all autopsies; it forms a small gelatinous button-like protrusion adherent to the cerebral aspect of the base of the skull, usually in the mesial plane of the clivus, 1 cent. behind the posterior margin of the pituitary fossa; it is without clinical significance except as a possible starting point for tumours.

Chordoma is a rare tumour of low malignancy derived from notochordal remnants. It usually occurs at one or other end of the

body, in the spheno-occipital or sacro-coccygeal regions. It tends to grow slowly, infiltrating and destroying surrounding tissues and even bone. It attains large size and eventually causes death. Exceptionally it grows rapidly, but it rarely gives rise to metastases.

The spheno-occipital chordoma generally arises in adults of thirty to forty years. Springing from the cerebral aspect of the clivus, it projects upwards into the cranial cavity and, eroding the bone, expands into the nasopharynx, the orbit, or the air sinuses. The sacrococcygeal chordoma may arise either in front of or behind the bones. It forms a slowly growing tumour which eventually may attain large size. When situated in front of the sacrum it tends to obstruct the gut and leads to interference with micturition.

Typically, the tumour is encapsuled and broken up into lobules by very dense fibrous trabeculae. The parenchyma is composed of bluish-white gelatinous tissue, often hæmorrhagic, and there are usually cysts containing mucoid fluid.

Microscopically, there are alveolar masses of cells of epithelial type, sometimes lacking clear definition and resembling a syncytium.

The most characteristic feature is the presence of large vacuoles, both in the cytoplasm and in the nuclei, so that the cells become swollen or bladder-like (physaliphoric). The vacuoles result from intracellular mucin-formation, and as the cells increase in size they discharge the mucin into the intercellular substance. In some tumours, especially those of slow growth, the greater part of the tissue may be replaced by masses of gelatinous material. Some parts of the tumour may assume sarcomatous characters.

Clinically, it is important to recognize the tumour, for though complete extirpation is not to be expected, local removal of the tumour or aspiration of mucoid contents has been followed by remarkable remission of the pressure effects.



FIG. 132. Chordoma. The tumour is composed of alveoli of vacuolated epithelial cells containing globules of mucin.

(By courtesy of Dr. W. A. Alexander and Mr J. W. Struthers.)

SACRO-COCYGEAL TUMOURS, CYSTS AND FISTULÆ

The complex nature of its development and the rudimentary structures which abound in its neighbourhood render the sacro-

NO DISEASES OF THE SPINE AND SPINAL CORD

coccygeal region very subject to the growth of tumours and cystic swellings. These are almost always congenital and are usually found in female infants; they are often incompatible with life, and when large may even cause impediment to parturition.

Classification is difficult, for the histological picture is remarkably varied. The simplest grouping recognizes two principal types, those due to anomalous development of the early embryo, and those arising from the persistence and growth of structures which under normal circumstances atrophy and disappear. In addition, inclusion dermoid cysts may occur in this region.

(1) **Anomalous Development in the Early Embryo.** This gives rise to various forms of parasitic inclusions, ranging from a solid teratoma up to a completely formed limb—an incomplete parasitic twin. It is believed that two embryonic areas form in the single blastomere, the one developing completely as the autosome, the other remaining ill-formed as the parasite. Two principal varieties of parasitic inclusions may be recognized:—

(a) Parasites composed of definite organs or their rudiments, portions of viscera, bones, or well-formed extremities. These are rare in man, and apart from the deformity give rise to no complications.

(b) **Sacro-coccygeal teratomata**, solid or cystic tumours arising either in front of or behind the sacrum and coccyx. These tumours are at first encapsuled and they may grow slowly or remain unchanged; but sometimes they assume sarcomatous characters. Microscopically, they have the features of a teratoma and include areolar and fibrous tissues, areas of cartilage, and mucoid, nervous and osseous tissues.

(2) **Persistence of Rudimentary Structures.** In the complex development of the hind part of the body there are several structures which may later give rise to tumours, cysts or fistulæ. Ventrally, there are the neurenteric canal, the post-anal gut, and the proctodæal membrane. The neurenteric canal is a tiny channel which in the early weeks of intra-uterine life connects the lower end of the spinal canal with the posterior termination of the gut. The portion of gut with which it communicates lies posterior to the point of communication between the gut and the invaginating proctodæum—post-anal gut. Tumours developing from these tissues are situated ventral to the sacrum and coccyx, though they may later be displaced downwards or dorsally. They are composed of closed vesicles lined by columnar-cell glandular epithelium, and they contain ropy mucus.

Congenital post-anal cysts and sinuses (pilonidal sinus) arise in the median plane in relation to the skin dimple at the tip of the coccyx, and are due to a defect in embryonic development. They are believed to arise from either a remnant of the spinal canal known as the coccygeal vestige, or (and more likely) from excessive traction on the skin caused by the retrogression of the tail bud (traction dermoid). The sinus is lined by skin, and hair may project at its orifice; and as a result of exudation into its lumen one or more small nodular cysts may develop subcutaneously. From the proximity of the sinus to the anus, infection and suppuration are apt to occur and fresh sinuses may be established at a higher level or laterally. The condition is chiefly

of importance because it is often confused with fistula-in-ano. As the sinus is lined with skin, healing cannot be secured unless the entire epithelial wall is excised.

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CHAPTER XV

DISEASES OF THE PERIPHERAL NERVES

NEURITIS DUE TO PRESSURE

APART from solution of continuity, the most important surgical lesions of the peripheral nerves are those due to pressure—*pressure neuritis*. There are three well-known examples of such neuritis which deserve individual consideration : (1) brachial neuritis due to pressure of an abnormal first rib or of a cervical rib, (2) traumatic ulnar neuritis, and (3) sciatica.

Brachial Neuritis from Rib Pressure

An abnormal first rib (or even a normal one) may give rise to brachial neuritis by pressure, but a cervical rib is a more usual cause.

A cervical rib is fairly common—1% or 2%—but symptoms occur in only about 5% of subjects in which it is present. Women suffer much more frequently than men (8 : 1), and the right side is more often affected than the left. The rudimentary rib arises in connexion with the transverse process of the seventh cervical vertebra (or, very rarely, the sixth). The formation and mode of articulation show great variation. In the type which commonly produces symptoms the rudimentary rib is fused with the vertebral body and/or transverse process and projects only slightly into the neck, but is prolonged as a dense fibrous cord which gains attachment to the periosteum at some part of the first rib. Sometimes it is more completely developed with a definite head, neck, and tubercle. It then articulates with the vertebra and laterally joins the first rib or its cartilage and sometimes the sternum.

The shape of a cervical rib varies. In some it is long, thin and pointed; in others it is broad and flat, and resembles the first rib, and may be grooved by the subclavian artery, and the lower part of the brachial plexus. The direction of the rib is important, because if it merely projects horizontally in a lateral direction it is unlikely to come in contact with the brachial plexus and subclavian vessels, whereas if it curves forwards these structures acquire a more intimate relationship with it. If the rib extends towards the first costal cartilage the scalenus anterior muscle in whole or in part may be attached to it.

The development of a cervical rib is from the anterior tubercle of the transverse process, which represents the costal rudiment of a cervical vertebra. According to Wood Jones, there is normally a "developmental antagonism" between the rib and the brachial plexus. The plexus is normally derived from the lowest four cervical nerves and the first thoracic nerve, and a brachial plexus in its normal situation is

believed to suppress its development. Sometimes the brachial plexus receives a large contribution from the fourth cervical nerve, and such a "prefixed" plexus is believed to favour the occurrence of cervical rib. In a similar way a "post-fixed" plexus widens the sulcus of the first thoracic rib, or interferes with the development of this rib to a greater or less extent.)

The development of pressure neuritis depends upon the relationship of the rib to the plexus. If the rib is small and projects laterally the plexus lies some distance in front of it, but if the rib is longer and curves forwards the lower trunk of the brachial plexus crosses it or its fibrous prolongation. Occasionally the middle trunk also crosses the rib.

Even a well-formed cervical rib does not necessarily predispose to pressure, especially if the plexus is "prefixed," but it is likely to do so with a normally constituted plexus. Similarly, the first thoracic rib does not usually exert pressure upon a normally placed plexus but may do so on a "post-fixed" plexus.

Predisposing Factors.

The predisposing factors in brachial neuritis from rib pressure include any factors that tend to stretch the lowest trunk of the plexus over either a cervical or the first thoracic rib. Probably

loss of muscle tone, such as occurs after acute illness, is an important factor, for it allows the weight of the arm to exert a dragging effect on the plexus and thus stretches it over the supernumerary rib or its fibrous extension. In this connexion it is of interest to note that symptoms have sometimes first appeared after the accessory nerve has been divided. Wingate Todd suggested that the dropping of the shoulder and the elongation of the neck that occur in adolescence, especially in women, may predispose to stretching of, or pressure on, the plexus, and possibly this is a reason for women suffering from brachial pressure neuritis more often than men. Thoracic respiration also may account for the greater frequency in women. It is very excep-



FIG. 133. Dissected specimen of bilateral cervical ribs. The right cervical rib articulates anteriorly with a protuberance from the first thoracic. On the left side the scalenus anterior muscle is seen inserted into the tip of the cervical rib, which is prolonged forwards to the sternum by cartilage. The relation of the brachial plexus to the cervical ribs is clearly shown.

(Museum of Royal College of Surgeons of Edinburgh.)

tional for symptoms to appear before the age of fourteen years ; most frequently they develop about the age of twenty. Typists, telegraphists, and seamstresses seem to be particularly susceptible. The onset of symptoms is often a sequel to some acute debilitating illness. There is evidence that the nerve pressure may result from constriction by the tendon of the scalenus anterior muscle, and division of the muscle at its insertion usually suffices for relief of the neuritis. Endoneural thickening with nuclear proliferation in the lower trunk of the plexus has been observed in some instances.

Effects. The effects of brachial neuritis from rib pressure are due mainly to pressure upon the sensory and motor fibres in the lowest trunk of the plexus, and probably to a varying extent to pressure upon the *rami communicantes* of the eighth cervical and first thoracic nerve.

Sensory disturbance is manifested by pain along the ulnar side of the forearm, and by paræsthesia and, later, small areas of anæsthesia in this region. Occasionally it occurs on the radial side of the forearm. Motor disturbance is manifested by difficulty in the delicate movements required in writing, piano-playing or typing and, later, by clumsiness in lifting small objects. Paresis of the intrinsic muscles of the hand may occur, and it may affect the muscles supplied either by the median or by the ulnar nerve. The paresis does not follow the nerve distribution strictly—for example, the abductor pollicis brevis and opponens pollicis may be affected, yet the flexor pollicis brevis, also probably supplied by the median nerve, may escape. At a late stage a typical “*main en griffe*” may develop.

The vascular phenomena, such as pallor and numbness of the fingers and in rare cases gangrene, are infrequent and inconstant. They have been attributed to pressure-irritation of the rib on the grey rami which join or have already become incorporated in the lowest trunk of the brachial plexus. It is, however, doubtful both on anatomical and pathological grounds whether so widespread a vascular obliteration as may affect the hand or even the entire arm can proceed from such an effect. More likely, as claimed by Lewis and Pickering and others, the constriction of the subclavian artery and local changes in its walls and lumen are responsible ; and certainly in those cases in which vascular phenomena predominate, either constriction, local thrombosis or calcification can be demonstrated in the subclavian artery. There is evidence that detachment of small thrombi from the subclavian artery and progressive intra-arterial clotting are responsible for the ischæmia in the hand and forearm. In many cases the subclavian artery is widened for some distance beyond the point where it crosses the cervical rib. This phenomenon bears some resemblance to the distal dilatation that follows experimental constriction of a large artery.

In some instances there is clear evidence that approximation of the clavicle to the first rib, as a result of faulty posture or injury, may be responsible for intermittent or continuous compression of the subclavian artery.

Traumatic Ulnar Neuritis

Apart from pressure of a cervical rib, the commonest cause of neuritis of the fibres of the ulnar nerve is injury to, or pressure upon

the nerve at the elbow joint. In most cases the condition follows a fracture in the region of the medial epicondyle, or it may follow arthritis, dislocation, exostosis of the ulna, contusion, and abnormal mobility of the nerve associated with recurrent displacement.

Platt, in an analysis of 252 cases of injury in the region of the elbow joint, found that neuritis developed in 9 instances, which indicates that the complication is relatively rare.

Ulnar neuritis sometimes develops soon after receipt of a fracture or other injury (**recent neuritis**), but more often there is a very long interval, even decades (**delayed neuritis**).

Recent neuritis is usually associated with a fracture of the medial epicondyle of the humerus or, in young subjects, with separation of its epiphysis. The neuritis may be due to contusion of the nerve as it lies posterior to the epicondyle, or to pressure by callus. In cases associated with separation of the medial epicondyle the signs and symptoms are often characteristic. There are swelling, and bruising, and tenderness over the medial side of the elbow, and a variable amount of numbness and anæsthesia in the skin of the ring and little fingers, whilst movement of the interossei muscles may be impaired.

Delayed neuritis usually develops in adult life. Fracture at the elbow joint is the most common predisposing cause, and it is characteristic of this form that many years elapse (it may be as many as thirty) before signs or symptoms appear. In some cases there is evidence of an old fracture which had occurred so early in childhood, and was so little disabling, as to leave no recollection of the accident.

In most cases the neuritis has been associated with a fracture of the *lateral* epicondyle of the humerus, in which there have been upward displacement of the separated fragment and faulty union in the position of cubitus valgus, in consequence of which the ulnar nerve is stretched or chafed. Probably changes in the elbow joint affecting the shape of the medial epicondyle determine the onset of neuritis.

When seen at operation the nerve is usually red and shows a spindle-shaped swelling, composed mostly of fibrous tissue.

In this type of neuritis the motor fibres appear to be more vulnerable than the sensory, for there may be atrophy of the interossei and the hypothenar muscles with only slight disturbances of sensation.

Sciatica

Two varieties of sciatica are recognized (1) primary or essential sciatica, and (2) secondary or symptomatic sciatica. The symptomatic variety is the more important from the surgical point of view.

(1) **Primary sciatica** may be due to neuritis of the sciatic nerve, and, apart from such definite predisposing factors as injury, alcoholism, etc., its ætiology is often difficult to determine. The disease affects rheumatic subjects who tend also to suffer from various forms of fibrositis. The lesion of the nerve is usually situated at the inter-vertebral foramina, taking the form of a peri-neural fibrosis or interstitial neuritis (radiculitis).

(2) **Secondary sciatica** is due usually to lesions which irritate or exert pressure on some part of the nerve, and sciatica should be regarded, in the absence of other evidence, as a symptom of some underlying condition rather than a specific disease. Thus, sciatica is often caused by disease in the pelvis, *e.g.*, malignant disease of the rectum or of the prostate, primary or secondary growths of the pelvis or the vertebrae, disease of the sacro-iliac joint or the hip joint, spondylitis deformans, prolapse of the nucleus pulposus of an intervertebral disc, abnormalities of the lumbar vertebrae, or affections of the nerve roots of the cauda equina (especially if it is bilateral).

The association of sciatica with either prolapse or herniation of the nucleus pulposus was referred to on p. 303. It is a compression neuritis due to impingement of a damaged intervertebral disc on one or more of the sciatic nerve roots as they emerge at the lumbosacral junction. Normally the nerve root lies loosely in the intervertebral canal protected by fat and loose areolar tissue. The posterior longitudinal ligament is in juxtaposition to the nerve anteriorly, but if retropulsion of the disc occurs (following, for example, hyperflexion of the spine), its protection is lost and the nerve root is subjected to pressure. In rare instances the injured disc projects across the middle line and produces sciatica bilaterally.

An injury of an intervertebral cartilage can only be proved conclusively by the appearances portrayed radiographically following intrathecal instillation of a contrast medium.

Sciatica is sometimes associated with abnormalities or postural deformities of the lumbar part of the vertebral column and with injuries at the lumbo-sacral region. The fifth lumbar vertebra exhibits many variations in its mode of articulation with the sacrum and in its fixation to the ilium. The commonest abnormalities concern the transverse processes and the inferior articular processes. The transverse processes are normally short and conical, but may be slender on one or both sides. They may articulate with the ilium or with the sacrum (sacralization). The inferior articular processes, instead of being crescentic and obliquely placed, may be flat and transverse. These architectural variations may not be associated with any pathological change, but in persons who engage in strenuous work they may lead to abnormal bony fixation of the vertebral column on one or on both sides, so that an undue strain is put upon the ligaments higher up or on the opposite side. Osteoarthritic changes may develop at the affected joints, and may be the real cause of the trouble. Commonly a functional scoliosis is acquired in order to lessen the strain. This may ultimately become a fixed deformity because the fifth lumbar vertebra becomes obliquely wedge shaped. The sciatica is then presumed to be due to pressure on the anterior ramus of the fifth lumbar nerve as it traverses the intervertebral foramen between the fifth lumbar vertebra and the sacrum. Normally, that ramus, which is the largest of the lumbar series, almost completely fills the foramen, and therefore any encroachment upon it, as by osteophytes, vertebral deformities, etc., readily causes compression.

TUMOURS OF PERIPHERAL NERVES

Structure and Development of Peripheral Nerves

The individual fibre of a nerve consists of an *axis-cylinder* (or *axon*) which is usually encased in a *myelin* sheath outside which is a continuous syncytium of cells, the *neurilemma sheath* (of Schwann). Nerve fibres are embedded in a fine reticulum—the *endoneurium*—are grouped cable-like by the *perineurium*, and maintained as a trunk by the *epineurium*.

The axon is a prolongation of a nerve cell, myelin (if present) is a product of the cell, and the neurilemma a derivative of the neuroectoderm emerging from the neural crest, as also, probably, are the supporting tissues endoneurium and perineurium.

Embryological and cytological researches, and Harrison's well-known experiments on frogs, make it certain that the epithelium of the neural crest is the progenitor, *inter alia*, of the posterior root ganglia,

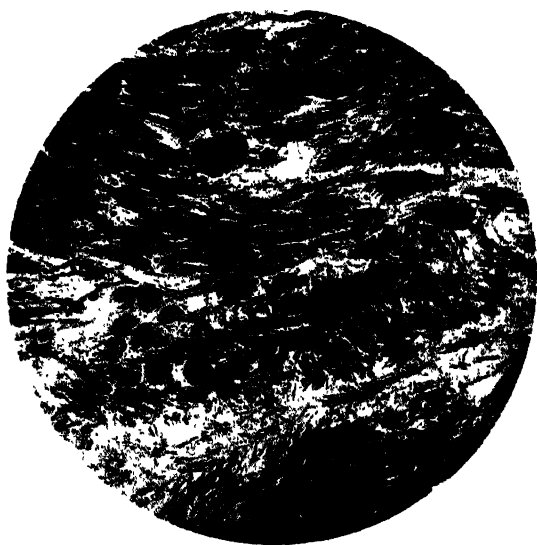


FIG. 184. Section of ganglioneuroma stained by Bielchowski method. Note ganglion cells and non-medullated nerve fibres.

the sympathetic nervous system (including the suprarenal medulla), the investments of nerves and the leptomeninx and choroid plexus

There is accumulated evidence that many tumours classed formerly as false neuromata are composed of undifferentiated nerve elements, and that the division of tumours into true and false neuroma may be discarded in favour of separate consideration of each well-defined type. There are well differentiated tumours in which the neural character is obvious, some in which it is supportable, many in which it is debatable. The following types will be considered :—

(1) **Neurinoma (False Neuroma.)**

This tumour was formerly regarded as a pure fibroma arising from the nerve coats, but its origin from the neurilemma sheath is now conceded except by a few. It is usually single, small, lightly encapsuled by the perineurium, and easily separated from the affected nerve trunk; it is, unlike a pure fibroma, prone to cystic degeneration. It usually affects nerves of the upper extremity and those in the subcutaneous tissues. It may occur intraspinally or intracranially.

Histologically, the major part of the tumour is composed of wavy bands of collagen, interspersed with elongated nerve fibrils. Whorls of fibres may be present, and in these zones clumping of the nuclei may occur to produce a familiar "palisade" effect. A reticulum stain displays crowds of fine fibrils which, it has been established, arise from the neurilemma sheath rather than from the endoneurium.

(2) **Neurofibromatosis ; (von Recklinghausen's Disease.)**

This condition is regarded as a developmental disorder of the supporting tissues of nerves rather than an example of new growth,

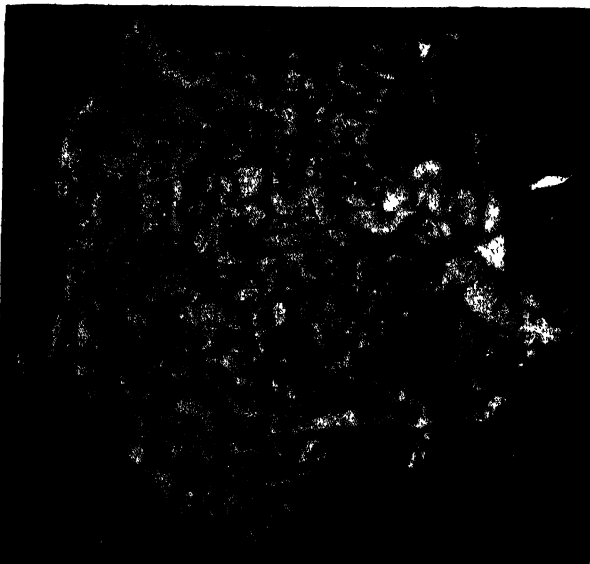


FIG. 135. Plexiform neuroma removed from the subcutaneous tissues of the lateral thoracic wall of a male child aged ten years. The tumour had gradually increased in size during five years. Diffuse neurofibromatosis and scoliosis were also present.

(Museum of Royal College of Surgeons of Edinburgh.)

although tumours (in the anatomical sense) may be one of its more obvious features.

Histologically, the characteristic feature of the disorder is proliferation of tissues, especially those of the nerve sheaths, in which both the fibrous and the neurilemmal elements participate in different degree and

with remarkable irregularity. In the tumour formations myxomatous changes are of common occurrence.

The disease, which is often familial, usually begins in adolescence, and frequently the first evidence is localized areas of pigmentation in the skin, followed later by overgrowth of nerve trunks or tumour, formations large or small, localized or widespread. Any of the nerves in the body, peripheral, cutaneous, sympathetic and cranial, may be affected. In some examples of the disease there are gliomata in the

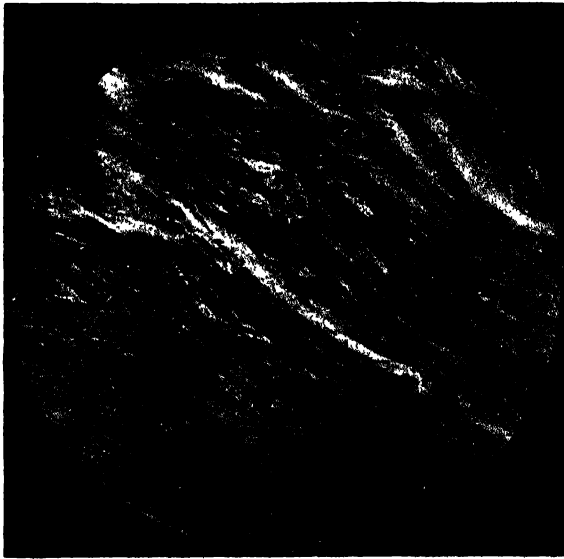


FIG. 136. Plexiform neuroma. Microscopic section stained by the Weigert-Pal method. (High power.) The tissue surrounding the nerve fibres is partly fibrous and partly of neurilemma origin.

(Museum of Royal College of Surgeons of Edinburgh.)

brain, in others multiple intrathecal tumours. In rare cases bilateral acoustic neuroma occurs, sometimes with tumours of the meninges and choroid plexus. The final outcome of the disease depends on the size and site of the tumours and upon the proclivity to malignant change.

The common ancestry of the different lesions is suggested by their complexity and remarkable blending in individual cases and the striking variations in groups of cases. The various lesions, will be discussed under the following headings :—

- (a) Generalized neurofibromatosis.
- (b) Plexiform neuroma.
- (c) Cutaneous neurofibromatosis (multiple soft fibromas of skin, molluscum fibrosum).
- (d) Elephantiasis neuromatosa.
- (e) Bilateral acoustic neuroma.
- (f) Primary sarcoma of nerves.



FIG. 137. Sarcoma of the posterior tibial nerve arising on a basis of neurofibromatosis. Note the greatly thickened nerve, which emerges near the lower extremity of the tumour. The other nerves of the limb showed the features characteristic of neurofibromatosis.

(Department of Surgery, University of Edinburgh.)

(a) **Generalized neurofibromatosis** varies greatly in its distribution. Any of the cerebrospinal nerves may be affected, as well as the ganglia on the posterior nerve roots, and the nerve fibres within the muscles and bones. The nerve roots within the spinal canal may also be affected, and this most often occurs in the cervical region and in the cauda equina. The affected nerves are diffusely and irregularly thickened so that small twigs may assume giant proportions; and, at intervals in the course of the nerves, growth may be exaggerated so as to form tumour-like swellings.

If one of the affected nerves is examined in transverse section the most notable change is the overgrowth of connective tissue within the primary bundles of the nerve. Certain bundles may be affected at one point and may be exempt at another. Some bundles may escape completely while others are markedly affected. The nerve fibres appear to traverse the substance of the swelling. The fibromatosis affects the endoneurium (the delicate connective tissue between the individual fibres of a nerve bundle), whereas the perineurium and the epineurium (outer sheath) are unaffected. There is no proliferation of the nerve fibres, and the only change which they undergo is compression and elongation. There is no degeneration and, therefore, no sensory or motor changes are observed.

In a considerable proportion of cases one of the tumours assumes malignant characters (so-called secondary malignant neuroma). Such transformation, by which the tumour assumes the features of a rapidly growing sarcoma, often follows injury or an attempt at removal.

(b) A **plexiform neuroma** is the result of diffuse fibromatous thickening of the branches of a nerve; the resulting swelling is palpable beneath the skin and may resemble thrombosed tortuous vessels. In more than half the cases there are manifestations elsewhere of generalized neurofibromatosis.

The commonest situations for a plexiform neuroma are the subcutaneous tissues of the head and neck, the large nerves of the extremities, and the autonomic plexus of the abdomen. The skin over

the tumours may show localized overgrowth and pigmentation, and the masses of thickened skin may become pendulous.

(c) **Cutaneous neurofibromatosis** (*mollusum fibrosum*) gives rise to multiple, soft, fibrous swellings of the skin, which vary in size from a pin's head to a plum or larger. They arise in connexion with the terminal filaments of cutaneous nerves. They may be sessile or pedun-



FIG. 138. Cutaneous neurofibromatosis. Note the large tumour of the right buttock and the patches of pigmentation. The woman's father suffered from neurofibromatosis.

(*Museum of Royal College of Surgeons of Edinburgh.*)

culated and are most numerous over the breast, back and abdomen. They may be very abundant on the scalp and the extremities, but the palmar surface of the hand and the sole of the foot escape.

In the majority of cases of cutaneous neurofibromatosis there is pigmentation of the skin, either in spots or diffusely disposed, and actual melanomata may be present. In addition, neurofibromatosis of the larger nerves is present in a large proportion of cases.

(d) **Elephantiasis Neuromatosa.** All intermediate grades may be recognized between *mollusum fibrosum* and elephantiasis neuromatosa; the two may coexist, and may be associated with generalized overgrowth of the nerves, and with plexiform neuroma.

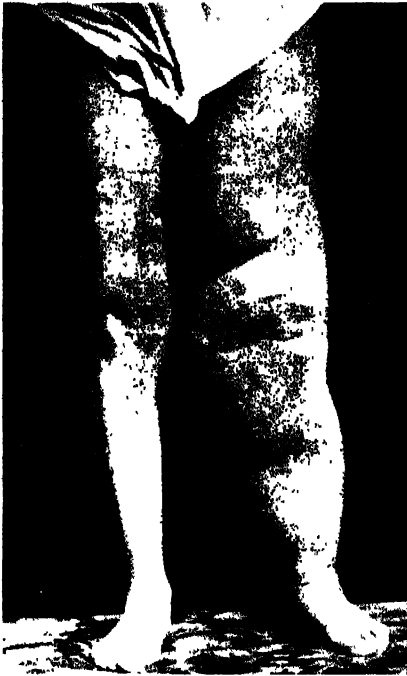


FIG. 130. Elephantiasis neuromatosa.
(Museum of Royal College of Surgeons of Edinburgh.)

The disease generally affects one of the extremities, especially the lower. It is of congenital origin and begins in a brown spot or mole, or in an area of neurofibromatosis, which may or may not be pigmented or hairy. The increase in size of the affected part is gradual, but may occur abruptly at puberty.

The skin and cellular tissues are enormously thickened and the subcutaneous fat is replaced by fibrous tissue. The subcutaneous tissues present an œdematous, glistening, greyish white appearance; in places they are soft and gelatinous, in others they are white, dry and fibrous. A variable number of tumours, isolated or in strings, may be present.

(e) **Bilateral Acoustic Neuroma.** In rare instances neurofibromatosis may be associated with bilateral acoustic

nerve tumours. The disease has a striking familial incidence, showing itself as a Mendelian dominant. Tumours of the dura and the choroid plexus may sometimes coexist.

(f) **Primary Sarcoma of Nerves.** A sarcoma usually originates in a nerve already the seat of fibromatosis, and the resulting tumour is usually of a spindle-cell or myxosarcomatous character: it possesses no appearances suggesting its neural origin. The tumour grows rapidly, is markedly radio-resistant, and recurs promptly after local removal. Metastasis is to be expected in at least 20% of cases.

(3) Ganglioneuroma.

This is the most highly differentiated type of nerve tumour and arises in connexion with the sympathetic trunks in the abdomen, neck, and the mediastinum. It commonly occurs in relation to the suprarenal gland. Histologically, it is composed of uni- or multi-polar giant cells in varying numbers scattered amongst nerve fibrils which may or may not be myelinated (Fig. 134). In rare instances ganglion cells are absent and the tumour consists of masses of amyelinated nerve fibres, a feature which suggests that nerve fibres may proliferate without the trophic influence of ganglion cells. Such tumours have been found in multiple form in the medulla, cord and pia mater, and in the mediastinum.

A ganglioneuroma commonly occurs in childhood. It varies in size

from a pea to larger than a melon. Some specimens are lobulated, others smooth and rounded. In appearance it resembles a fibroma or a lipoma. It is unattended by any symptoms suggestive of a nervous origin or structure, and such pathological effect as it produces is due to pressure.

(4) Sympathicoblastoma (Neuroblastoma).

This tumour develops from immature cells of the sympathetic nervous system, and is therefore common in the first years of life. There is great variation in the structure of the tumour. The most undifferentiated (which nearly always occurs in the region of the kidney) is composed of lymphocyte-like cells, often arranged like staphylococci, and intensely argentophilic. Rosette formations may be present at the periphery of the tumour, but there are no fibrils. Such tumours are rapid growing, reach a large size and metastasize widely. The more differentiated types (which also are commonest in relationship to the suprarenal gland, but may occur in the neck, the cœliac ganglion and other sites) are usually smaller and are composed of more differentiated cells often of larger size than in the undifferentiated with more numerous rosette formations, nerve fibrils, axis cylinders and ganglion cells. They may metastasize by the blood or lymph channels. It has been observed repeatedly that if ganglion cells are present in the parent tumour they are not found in metastases.

It has been observed that an undifferentiated tumour may during years gradually change its character and become differentiated, *i.e.*, the normal evolutions of the sympathetic nervous system are reproduced within the tumour.

(5) Stump Neuroma.

A traumatic or stump neuroma arises in the divided nerves after amputation. The occurrence of a small bulbous or fusiform swelling at this situation is normal, but in some circumstances the "neuroma" assumes a large size, especially if there has been infection.

The bulbous swelling consists of fibrous tissue, newly formed unmyelinated nerve fibres in irregular formation, and a syncytium of cells derived from the neurilemma sheath.

Bulbous enlargement of the nerve trunks may also follow repair of a nerve after division, and prolonged irritation, as in traumatic ulnar neuritis.

(6) Glomal Tumour (Glomangioma).

This is a tumour of one of the cutaneous glomera, the specialized arterio-venous anastomoses which are believed to have the effect of regulating the temperature and maintaining the circulation in peripheral parts exposed to cold.

The normal glomus consists of a much convoluted, modified arteriole communicating directly with a vein. It has a rich perivascular nervous

network and is believed to be capable of independent dilatation and contraction. It probably exercises its function by acting as a circulatory shunt, diverting blood into or away from the local capillary network.

The glomera are most numerous in the extremities, especially in the nail-beds, and tumours of the glomera are also more common in these sites. The tumour is of slow growth and encapsuled. It may be symptomless or give rise to pain of a burning or bursting nature, originating in the tumour and sometimes radiating widely.

Pain is most common in subungual tumours, and may be brought on by pressure or light touch, or even by a change of temperature.

Microscopically the tumour is an angioneuromyoma. There are cavernous blood spaces containing red cells or thrombus, thick-walled blood vessels showing proliferation of the muscle cells of the media, and numerous nerve twigs bearing hyperplastic perineurium. A characteristic feature is the presence of masses of *glomus cells*, cuboidal cells normally found beneath the endothelium of the vascular channel of the glomus. In the tumour these cells lie in coherent perivascular sheets. They are of uniform appearance, cuboidal in shape, with rounded hyperchromatic nuclei and distinct limiting membranes.

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CHAPTER XVI
DISEASES OF THE THORAX
DISEASES OF THE PLEURA
PNEUMOTHORAX

KNOWLEDGE of the phenomena of pneumothorax in its various forms is essential for the proper appreciation of the effects of diseases of the lungs and pleura, and for the safe conduct of measures for their relief.

In health, the parietal and visceral layers of pleura are virtually in contact; for the pleural cavity is merely a capillary interval containing the film of lymph that moistens their surfaces. They are kept in contact by the distension of the lung under atmospheric pressure; and, owing to traction of the elastic tissue of the lung, the pressure of the potential pleural cavity is negative. During the inspiratory expansion of the chest the pressure diminishes till it is -7 mm. to -9 mm. of mercury at the end of inspiration; and air enters through the air passages and distends the lung still further to prevent a vacuum. In expiratory contraction of the chest, which is normally a passive movement, the lung shrinks by its inherent elasticity and partially evacuates its air; and the intrapleural pressure rises, but even at the end of expiration it does not equal the atmospheric pressure unless the glottis is closed. Deep inspiration may increase the negative intrapleural pressure to -80 mm. Hg. and a forceful expiratory effort, such as coughing, produces positive readings as great as $+50$ or $+60$ mm. Hg. The effects of alteration of the lung volume upon the intrapleural pressure will be considered more fully when the diseases that produce them are dealt with.

When air is present in the pleural cavity the condition is called **pneumothorax**. In **open pneumothorax** the air has free entrance and exit through a wound in the chest wall. In **closed pneumothorax** the air has neither entrance nor exit. In **valvular or tension pneumothorax** the air may enter but not escape from the pleural cavity. Each variety requires separate discussion.

Open Pneumothorax

Open pneumothorax may be the result of an injury to the thoracic wall, or it may be produced deliberately in operations on the thoracic viscera. When an opening is made in the chest wall, air rushes into the pleural cavity, and the pressure within it rises. The lung—no longer responsible for the prevention of a vacuum—shrinks or collapses, owing to its elasticity, to the extent of the space occupied by the invading air. The only air effectual for oxygenating the blood is

that which enters by the air passages, and with ordinary respiration that would now be less than the normal requirement by the amount which enters through the opening in the chest wall; therefore, to maintain adequate oxygenation the patient must increase either the rate or the depth of respiration. In health a small opening is usually well tolerated, for only a little air enters, and a healthy system has strength to cope with the difficulty and can accommodate itself to the change. The normal requirement at each inspiration is approximately 500 c.cm. of air (the *tidal air*), whereas, the maximum amount a healthy adult can inhale is almost 4,000 c.cm.

If the opening in the chest wall be large, the condition may be serious. The lung shrinks to one-third or less of its original bulk, and the partial or complete collapse of the alveoli puts even more than two-thirds of it out of effective action. Also, the other lung suffers reduction, for the mediastinal septum—in health (especially in young subjects) a soft and yielding partition made up chiefly of the heart and great vessels—is *pushed* by atmospheric pressure towards the sound side with each inspiration, to help to prevent the formation of a vacuum on that side. The septum moves back on expiration. This to and fro movement is accompanied by a mediastinal flutter, *i.e.*, a tremulous quivering of the structures in the septum, and since the heart is implicated in these movements they may be associated with a rapid pulse and shock. In addition, if a large open pneumothorax is long maintained the heat-loss from the body is considerable, and, as a result of the changed pressure relationship in the pleura, the return of venous blood to the heart may be impeded. In a large pneumothorax the air taken into the opposite lung is derived chiefly from the exterior, but also, in a small part, from the collapsed lung, and during expiration the air is expelled through the trachea and partly into the collapsed lung, which becomes expanded to an extent proportionate to the expiratory effort. The movements of the lung on the side of the open pneumothorax are therefore reversed, since the lung collapses during inspiration and expands during expiration (*paradoxical respiration*). The re-breathing of vitiated air which results from the paradoxical respiration leads to dyspnoea and demands violent respiratory movements to neutralize its ill effects.

These untoward effects of open pneumothorax are seldom witnessed except in severe injuries to the chest, especially if already there is a considerable degree of shock. They are not usually experienced in operations within the pleura provided the opposite lung is healthy and the patient's vital capacity¹ is fairly normal. A large opening into the pleura, in which the lung collapses, can be made with impunity. Even though the patient lies on the normal side respiration is undisturbed. A further safeguard against the possible ill-effects of open pneumothorax is provided by the modern methods of anæsthesia which ensure delivery of so high a concentration of oxygen to the lungs that anoxæmia is not likely to occur if the airway is unobstructed.

¹ The *vital capacity* is a valuable indication of the respiratory reserve. It is defined as the maximum amount of air which can be exhaled after a maximum inhalation: on the average it is about 3,500 c.cm.

Valvular and Tension Pneumothorax

This form of pneumothorax may be urgent. It is usually attended by considerable shock and may lead to fatal asphyxia. The commonest cause is rupture of the wall of a superficial vomica in a tuberculous lung and the consequent establishment of a valvular communication between the air passages and the pleural cavity. The pleural cavity becomes greatly distended with air and sometimes purulent material. The wall of a tuberculous cavity may rupture during the treatment of pulmonary tuberculosis by artificial pneumothorax, especially if adhesions between the pulmonic and parietal pleura are situated over a cavity or an active focus of disease.

Other causes of tension pneumothorax are :—

- (1) Rupture of an emphysematous bulla. This may take place in an apparently healthy person. Usually the air is rapidly absorbed, but recurrence, occasionally on the opposite side, is not uncommon.
- (2) Stab or bullet wounds that penetrate the lung. In such cases the condition is complicated by hemothorax.
- (3) "Sucking" wounds of the chest wall.
- (4) Escape of air from a divided bronchus (bronchial fistula) after an operation on the lung.

When a large quantity of air is confined within the pleural cavity the pressure is usually greatly raised, and as high a reading as 20 mm. of mercury may be registered. Not only is the lung on the affected side compressed but the mediastinum is displaced towards the sound side, and (when the right side is affected) the direct pressure on the great veins and the auricle may impede the blood flow to the heart.

Closed Pneumothorax

This form of pneumothorax is usually produced artificially as a therapeutic measure to secure rest for a tuberculous lung, air being introduced into the pleural cavity to cause partial or complete collapse (artificial pneumothorax).

By the introduction of air the intrapleural pressure is modified and the expansibility of the lung is proportionately decreased. If, however, the opposite lung is healthy, complete pulmonary collapse may be tolerated without any ill effects, unless the mediastinal septum is unduly flexible, when the respiratory capacity of the opposite lung may be seriously affected by displacement of the septum. In such cases the intrapleural pressure on the side opposite the pneumothorax may be actually raised, and the expansion of the lung may be so hampered that dyspnoea and cyanosis result.

Air in a closed pneumothorax disappears completely in a few weeks and sometimes in a few days. On this account early experimenters with artificial pneumothorax substituted nitrogen for air in the belief that it would disappear less rapidly. It is now known that, owing to the diffusion of gases between the alveoli and the pleural cavity, the composition of the contents of a pneumothorax, even if pure nitrogen or oxygen has been introduced, soon becomes the same as that of alveolar

air. For that reason it is now customary to use air for artificial pneumothorax rather than nitrogen, because of its greater convenience.

It has been calculated that the adult pleural cavity will hold 8,000 to 4,000 c.cm. of air. Its rate of absorption is very variable, but, on an average, 80 to 100 c.cm. are absorbed per diem. The rate of absorption is increased by bodily activity, and is diminished by advanced disease of the lung and by pleurisy, whether past or present.

ACUTE EMPYEMA

Acute inflammation of the pleura is often attended by an effusion of serous or sero-fibrinous fluid into the pleural sac, and when such an effusion becomes purulent the condition is called *empyema*. It is the commonest surgical disease of the thorax at any age.

Ætiology and Sources of Infection

Infection may reach the pleura by any of three avenues : (1) directly from the lung, mediastinum or abdomen ; (2) by the blood stream ; (3) through perforating wounds of the chest wall.

(1) **Direct Infection from the Lung, Mediastinum, or Abdomen.** The commonest cause of empyema is spread of infection from a lung which is the seat of pneumonia—either lobar pneumonia or bronchopneumonia. It may occur during the acute stages of the pneumonia (synpneumonic), especially in bronchopneumonia, but more often it occurs when the pneumonia is undergoing resolution (metapneumonic).

The micro-organism is usually the same as that of the initial pneumonia. In lobar pneumonia it is generally the pneumococcus ; in bronchopneumonia it is sometimes a streptococcus, which may be of a hæmolytic type. Sometimes the two organisms coexist. As the reaction of the pleura differs in many respects in pneumococcal and streptococcal infections, it is important, especially from the point of view of treatment, to differentiate between the two types (see below).

Occasionally empyema follows rupture of an acute lung abscess on the pleural surface, and in such cases the pus is often putrid and contains anaerobic organisms, such as *Cl. Welchii*, spirochætes, and large fusiform bacilli. In this type of empyema the pleural cavity often contains air derived from the lung (pyopneumothorax). Putrid empyema is, as might be expected, a common occurrence after operations for bronchiectasis.

Empyema frequently follows suppuration in the peritoneal cavity. It is most common as a complication of perforated duodenal or gastric ulcer, suppurative appendicitis, or abscess of the liver. It is sometimes preceded by a subphrenic abscess. The avenue of infection in such circumstances is probably the subdiaphragmatic lymph plexus. The right pleural sac is more often involved than the left, and the *bacillus coli* is the organism commonly present.

In rare cases empyema follows those infections of the mediastinum that arise, for example, from osteomyelitis of the vertebræ, from perforating wounds of the œsophagus, or from cellulitis of the neck. In such cases the infecting organisms are generally streptococci or

staphylococci, sometimes accompanied by other bacteria, and the disease takes a rapid course and usually is fatal.

(2) **Infection by the Blood Stream.** Empyema of hæmatogenous origin is generally streptococcal or staphylococcal. Usually it is a complication of acute tonsillitis, scarlet fever, puerperal sepsis or pyæmia. Usually there is an intermediate pulmonary lesion such as multiple small abscesses at the surface of the lung.

(3) **Infection through Penetrating Wounds.** Empyema from direct infection may arise from bullet or stab wounds or after operations on the thoracic viscera. The presence of effused blood in the pleural cavity predisposes to infection.

Types of Empyema

The pathological changes in the pleura and the lung vary with the organism responsible, and the differences between pneumococcal and streptococcal infection are sufficiently great to warrant separate descriptions.

Pneumococcal Type. Pneumococcal empyema generally occurs a week or more after the crisis of lobar pneumonia: the Type I organism is most often responsible. In the early stages the pleural cavity contains a variable amount of sero-fibrinous or sero-purulent fluid. It is the infection of a residual pleural effusion. The pleura is congested and oedematous and lacks its normal lustre. On the surface of the lung, especially over the lower lobe behind, an exudate of purulent lymph adheres loosely to the parietal pleura. According to the stage of resolution of the antecedent pneumonia the lung may be firm and solid, or spongy and elastic.

At quite an early stage the pleural effusion becomes thick and definitely purulent; the pus is greenish-yellow in colour and generally contains semi-solid coagula of fibrinous purulent lymph. The effusion gravitates to the lower and posterior part of the pleura. It varies from 20 c.cm. to over a litre. Adhesion of the parietal and pulmonic pleura around and beyond it circumscribes it at so early a stage that it is technically an abscess. It is characteristic of this type of empyema that the inflamed parts of the pleura rapidly become thickened, and if evacuation of the pus is deferred too long the lung may fail to re-expand.

Pneumococcal empyema usually develops after the crisis of pneumonia, *i.e.*, when obliterated alveoli are resuming their function, and when the patient is recovering from the immediate effects of the disease. The effusion early becomes circumscribed by adhesions and then thoracotomy can be safely undertaken, for it is not attended by the dangers of an open pneumothorax.

Streptococcal Type. This variety of empyema results from a generalized pleuritis, which may arise coincidentally with or some time after the onset of streptococcal bronchopneumonia. The pleura, especially the pulmonic layer, shows widespread congestion and sometimes discrete areas of hæmorrhage. The effusion tends to be larger than in the pneumococcal variety, and is at first greenish-brown or even hæmorrhagic; gradually it becomes sero-fibrinous, and only in the

course of a week or more does it become purulent. The pus is generally much thinner and less green than in pneumococcal empyema, and fibrin, if present, is in the form of shreds or small flakes.

The large size of the effusion and generalized and acute nature of the pleurisy in the early stages retard the formation of adhesions, but when finally they do occur, the empyema does not differ from the pneumococcal type.

The effusion remains thin for a long period and adhesions are late in forming. Early thoracotomy therefore imposes the dangers of an open pneumothorax at a time when the vital capacity is taxed to the utmost, and drainage is secured only at the cost of putting out of action what relatively little pulmonary tissue is still functioning. Too early drainage therefore sometimes promotes a fatal issue. In this variety of empyema (especially if it is associated with broncho-pneumonia), the treatment is at first expectant, but if the effusion is so large that it embarrasses respiration, it may be aspirated. Open drainage is resorted to later, when the general condition has improved. The most convenient indication that the time for open drainage has come is the discovery of thick pus on aspiration, for almost certainly by the time that the exudate has changed from its initial sero-fibrinous nature to a purulent character the pneumonia will be resolving, the patient's vital capacity will have increased, and pleural adhesions will have formed. In all cases, general and local conditions should determine the appropriate time for, and method of, intervention.

Effects of Empyema

A large empyema may cause considerable compression of the lung, and may push the heart, great vessels and trachea towards the opposite side.

If the pus is not evacuated, the exudate becomes organized and the pleura greatly thickened; the walls of the empyema cavity may be 25 mm. or more in thickness and may become calcified. If the empyema is not drained and if the exudate is large the lung is compressed into a small fibrous mass against the vertebral column, where it is fixed by the thickened pleura, and much deformity of the chest may follow.

The pus of an undrained and active empyema may burrow into the lung, or it may perforate an intercostal space (*empyema necessitatis*). External rupture usually occurs at the front of the chest close to the sternum.

Special Types of Empyema

Interlobar Empyema. Occasionally a pleural effusion is confined to one of the pulmonary fissures, especially in the right lung; and when suppuration occurs a circumscribed abscess results. Such an empyema is usually small and may rupture into the pleural cavity, but more often opens into one of the large bronchi, after which its walls become approximated from expansion of the surrounding lung, and spontaneous cure results. In rare cases an interlobar empyema becomes organized and its capsule calcified.

Mediastinal Empyema. A purulent pleural effusion may become localized in that portion of the pleural cavity that abuts on the mediastinum, and may simulate a collection of pus in the mediastinum (Fig. 140).

Apical Empyema. In rare instances an empyema may be localized in the apical region of the chest, either in front, behind, or laterally. It possesses no special features except that cardiac pulsation may be transmitted to it, especially when it is situated on the left side.

Bilateral empyema sometimes occurs as a complication of broncho-



FIG. 140. Acute empyema confined to the mediastinal aspect of the right pleural cavity.

pneumonia in children or of influenza in adults. It calls for special consideration in regard to treatment.

Pyopneumothorax is most often associated with tuberculosis, but may follow rupture of an acute lung abscess into the pleura. The infecting organisms are usually of a virulent type; pleural adhesions have not yet formed and the disease generally takes a rapid course. If the aperture in the lung is valvular a tension pneumothorax will result and give rise to great distress in respiration. A broncho-pleural fistula may persist after the contents of the empyema have been evacuated.

Tuberculous pyopneumothorax is usually due to breaking down of tuberculous foci at the periphery of the lung or to rupture of the wall

of a tuberculous cavity. The condition not infrequently arises during treatment of pulmonary tuberculosis by artificial pneumothorax. Superadded pyogenic infection, sometimes putrid, is not uncommon.

Rare Forms of Pleural Effusion

Chylous effusion (chylothorax) is uncommon. It may arise from injury to the thoracic duct and pleura in fractures and gun-shot wounds, or from injury during operations on the œsophagus. The fluid tends to accumulate rapidly and may lead to fatal asphyxia. At first it is often bloodstained, later it is yellowish-white and the microscope reveals fat droplets and a variable number of lymphocytes.

Pseudo-chylous effusion is the name given to opalescent and milky effusions sometimes associated with malignant diseases of the lung and pleura.

Biliary effusion is very rare. It occurs as a complication of suppurative lesions of the liver or the bile ducts, after the establishment of a fistulous communication through the diaphragm.

Cholesterol effusion is exceedingly rare. The exact cause is unknown. It is usually preceded by a serous effusion which may be general or localized. The fluid is usually of brownish colour and contains the characteristic rhomboidal crystals of cholesterol. The surface of the pleura may be gritty from the accumulation of cholesterol.

CHRONIC EMPYEMA

In ordinary circumstances the walls of an empyema cavity are approximated mainly by expansion of the lung and, to a less extent, by ascent of the diaphragm, shrinkage of the chest wall, and deflection of the mediastinal septum. The opposed surfaces of the parietal and pulmonic pleuræ bounding the cavity adhere to each other owing to the sticky character of the effusion that covers them. Organization takes place in this effusion, binding the two pleural layers together and permanently obliterating the empyema cavity. These natural processes of obliteration and healing may be incomplete, and the space persisting between the pulmonic and parietal pleuræ is known as a chronic empyema cavity.

Ætiology. The chief factors which lead to this chronic state are (a) persistence of infection, and (b) failure of the lung to expand. Either or both of these factors are usually attributable to one or more of the following causes :—

(1) Undue delay in the drainage of an acute empyema, particularly one of pneumococcal type, which allows the thickened pleural surfaces to become organized and rigid, and thus prevents re-expansion of the lung.

(2) Too early drainage of an acute empyema, particularly one of the streptococcal type, in which absence of adhesions permits complete collapse of the lung.

(3) Inadequate drainage through a small or tortuous or improperly placed opening.

(4) The presence of portions of dead rib or of foreign bodies, such as a rubber drainage tube.

(5) The coexistence of disease in the lung, for example, chronic interstitial fibrosis, which interferes with expansion of the lung.

(6) The presence of tuberculosis, abscess or new growth in the lung, or of suppurating cysts in the lung or mediastinum.

(7) The presence of a broncho-pleural fistula, which maintains infection and also reduces the inspiratory expansion of the lung.



FIG. 141. Calcification in the walls of a chronic empyema.

Morbid Anatomy. When an empyema cavity fails to heal a sinus usually persists, and pus may escape from it continuously or intermittently. It frequently happens that the wound in the parietes heals temporarily, and after a variable period reopens and pus escapes again. Healing and discharge may alternate during many months or years, and in such cases the accumulation of pus in the pleural cavity may be attended by pain, fever, and a variable degree of systemic disturbance.

The size and shape of a chronic empyema are very variable. The cavity may be quite small, or it may involve practically the whole side of the thorax. Usually the cavity is in the paravertebral gutter,

and is large below and tapering towards the apex of the chest. Smaller cavities may communicate with the main chamber like diverticula. }

The walls of the cavity, formed by the pulmonic and parietal pleura, are often greatly thickened and tough. If the cavity contains no pus the surfaces may be quite smooth and dry; but when infection remains and there is a collection of pus the pleural surfaces are coated with a purulent exudate of lymph or with soft œdematous granulation tissue. In old-standing cases the exudate may undergo calcification so that the cavity is lined with a calcareous shell (Fig. 141).

Operation offers a favourable opportunity for studying the characters of the tissues surrounding a chronic empyema. The ribs are usually closer together than in a healthy chest and may overlies one another; if there have been previous operations they may be fused. The bone varies in density according to the duration of the empyema; in fairly recent cases the periosteum is thick and more vascular than normally and the bone is less dense; in old-standing cases the ribs are sclerosed. The parietal pleura may be three or more centimetres thick. In recent cases it is often œdematous and vascular and bleeds freely; in older cases it is extremely dense and unyielding, and may be as hard as leather. Areas of calcification (or even of bone) may be present in the thickened membrane. When the diaphragmatic pleura is affected, the diaphragm is usually fixed in an elevated position. When the pericardial pleura is involved, the resulting adhesions may embarrass the action of the heart.

The pulmonic pleura also is thickened, though seldom to such an extent as the parietal, and the thick and rigid pleura interferes with the expansion of the lung. If incisions are made into the thickened pulmonic pleura a plane of cleavage between the original pleura and the organized exudate may be discovered, sometimes easily, usually with difficulty.

In chronic empyema the lung, though reduced in size, is often capable of full expansion if liberated from its adhesions. If the cavity is very large the lung may be reduced to very small size and fixed against the bodies of the vertebræ. In a few cases the lung becomes the site of atelectasis and fibrous induration, and is then incapable of expansion.

If chronic empyema is of recent origin, and if a considerable degree of infection persists, healing may be promoted by adequate drainage and by measures to encourage re-expansion of the lung. When the cavity is of old standing, mechanical factors are the chief barrier to healing. Obliteration of the cavity may be attempted by stripping the thick pleura from the lung (*decortication*), but if (as is usual) no plane of cleavage is found the rigid outer walls of the cavity require removal, so that the muscles and skin may adhere to the pulmonary wall of the cavity.

Effects of Chronic Empyema. In young subjects the fibrosis and consequent contraction induced by a chronic empyema are apt to interfere with the development of the thorax and to cause great deformity. The affected side becomes shrunken and immobile, and the intercostal spaces are narrowed, while the diaphragm is elevated and

the mediastinum is deviated towards the affected side. As a secondary result an extensive scoliosis may develop.

The existence of a chronic empyema is sometimes compatible with fair health; but often it leads to toxæmia, and eventually to anæmia, emaciation and amyloid disease. As in other thoracic suppurations, clubbing of the fingers is apt to develop. An occasional fatal complication is an abscess of the brain.

DISEASES OF THE LUNG

MASSIVE COLLAPSE OF THE LUNG—Atelectasis

Collapse of part of a lung or of the whole of it is usually due to agencies that exert pressure on it from without, and the commonest of them are pleural effusion and pneumothorax. In those circumstances collapse of the lung occurs *passively* in response to the external pressure, and the extent of the pulmonary collapse is, of course, proportionate to the pleural space occupied by the compressing agent, and the lung, though partly collapsed, remains capable of a limited amount of respiratory excursion. But, in the condition known as **massive collapse**, the lung, or part of it, is rendered airless from intrinsic causes, and undergoes *active* collapse for a variable period. The negative intrapleural pressure, exaggerated by the sudden shrinkage of the lung, maintains the apposition of the lung to the parietes, and to prevent the formation of a vacuum the mediastinal septum is drawn to the affected side. The cause of the pulmonary deflation is absorption of the alveolar air after obstruction of the bronchi of the affected part of the lung. Such collapse is commoner on the right side and most often affects part of, or the entire lower lobe of the lung.

Massive collapse is most frequent as a complication following surgical operations, especially those on the abdominal viscera, but it has occurred after fractures of the limbs or injuries to the thorax, and occasionally in association with diseases of the lungs, such as bronchial tumours and the pressure of tuberculous glands at the lung root. It may follow any form of anæsthesia, even local. The subjects of this complication are usually strong young adults, and the greatest number of cases have followed operations on the appendix, and the gall bladder, and those for inguinal hernia.

Mode of Onset and Progress. In the most obvious cases the onset is sudden—often within forty-eight hours of operation—and gives rise to an alarming crisis, evidenced mainly by severe dyspnœa and pain in the chest. Sometimes the symptoms are less dramatic, and in others are so slight that the condition may not be suspected. Often there are premonitory signs or symptoms, such as flushing of the face, tightness of the chest and cough. The temperature rises suddenly to about 101°, and the pulse rate is increased.

During a severe attack the appearance and attitude of the patient are characteristic. There is dyspnœa accompanied by cyanosis. The patient lies on, or inclines towards, the affected side. Cough is slight and sputum is scanty or absent. The patient may remain in distress

for 12 to 36 hours or longer; relief may come abruptly after violent coughing, or after a sudden movement. As the attack subsides a considerable quantity of purulent tenacious mucus may be expectorated.

During the attack the affected side of the chest is almost immobile, and is flattened, and the ribs are approximated. Deflection of the heart towards the side of collapse is one of the most characteristic signs. On percussion there is an area of dullness corresponding to the portion of lung collapsed, and the breath sounds and vocal fremitus are diminished. The physical signs may alter from time to time, and tubular breathing and coarse crepitations may be present as the attack terminates.

The collapsed portion of the lung is represented in a radiogram by

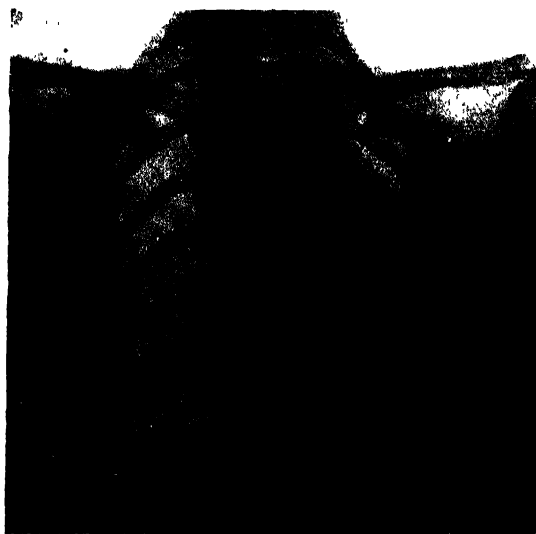


FIG. 142. Post-operative massive collapse of the lung. A radiogram two days after the onset of massive collapse following operation for perforated gastric ulcer. Note the increased density at the left base, and the deviation of the heart and the trachea to that side.

a uniformly opaque shadow. The mediastinal septum, consisting of the heart, trachea, etc., is deviated towards the affected side, the ribs are approximated and the diaphragm is elevated. The unaffected side shows abnormal translucency from "compensatory" emphysema (*see* Fig. 142).

The intrapleural pressure on the affected side is reduced to -15 or -20 mm. of mercury, and respiratory movements effect practically no change in the reading.

Causation. There has been much discussion as to the exact cause of massive pulmonary collapse, and many theories to explain its origin have been advanced. Argument has been centred chiefly around the nature and the mode of production of the bronchial obstruction that culminates in atelectasis. The view most widely held, and most tible of proof, is that the collapse of the lung is due to the obstruc-

tion of one or several of the larger bronchi by tenacious exudate, such as is likely to accumulate when there is already some degree of bronchial catarrh and respiration is impeded by diminished movement of the diaphragm and abdominal muscles. The bronchial obstruction is followed by the absorption of most of the alveolar air, and the unsupported vesicles of the lung collapse.

Other theories, not always based on observation, have attributed the bronchial obstruction to reflex spasm of the bronchioles of one region of the lung, to oedema of the bronchial mucous membrane (possibly of allergic origin), and to circulatory changes in part of the lung.

It is not surprising that massive collapse may be associated with or followed by bronchopneumonia or even bronchiectasis. The mechanical obstruction of the chief bronchi favours stagnation of secretions and propagation of infection, and the negative pressure within the collapsed lung tends to draw the exudate still more distally within the bronchial passages.

POST-OPERATIVE PULMONARY EMBOLISM

Statistics of large hospitals show that pulmonary embolism is responsible for death about once in every thousand operations. But non-fatal cases are much more frequent and constitute a fairly common post-operative pulmonary complication, especially in stout subjects after the age of forty-five years.

The severity of pulmonary embolism depends principally on the degree of occlusion of the pulmonary artery and/or its branches.

There are three familiar types of pulmonary embolism: (1) Those in which there are no premonitory symptoms and death occurs rapidly or sometimes instantaneously. (2) Those in which there is an acute and sudden crisis with pain in the precordial region, severe dyspnoea and cyanosis, and the patient survives for several minutes or even a few hours, or may recover. (3) Those in which there is sharp pleuritic pain, dyspnoea, and later, hæmoptysis from hæmorrhagic infarction of part of the lung; in these, however, the outlook is favourable, even though there should be a second attack in the same, or the opposite, lung.

Pulmonary embolism is most frequent after abdominal operations, although it may follow injuries or childbirth. It is most apt to follow operations on the pelvic organs, such as hysterectomy and prostatectomy, and operations on the upper part of the abdomen, but it may follow operations for hernia, appendicitis, and many other affections. Embolism is not common after operations on the upper part of the body.

Emboli too small to cause infarction, and therefore almost symptomless, are commonly found post-mortem in patients dying from a variety of surgical or medical diseases.

The time of onset of pulmonary embolism ranges from 24 hours to 8 weeks after operation, but the usual time is about 10 days—that is when the convalescent patient begins to get out of bed and

move about. Premonitory signs and symptoms are generally absent; usually the patient has made a satisfactory recovery from operation, and the embolism is an unexpected complication; but in a number of instances the patient has been rather restless, has slept badly, and has had slight rises of temperature from time to time, and recovery from operation has not been so uneventful as expected. The subjects



FIG. 143 Pulmonary embolism. Embolism occurred eight days after an operation for ventral hernia in a woman aged sixty-two years, who survived the sudden onset of pain and dyspnoea for fifteen minutes. The right iliac vein was the site of thrombosis. Note the coiled embolus in the right ventricle.

of fatal pulmonary embolism are very often "poor lives" and suffering from debilitating illness.

Post-mortem examination of fatal cases shows that the trunk of the pulmonary artery or the roots of its two branches are completely or almost completely blocked by a firm clot or clots, often several inches in length. Other clots, often coiled, attached to or separate from the main clot, may be in the right ventricle, or extend even into the inferior vena cava (Fig. 143). In other instances one or other of the branches

of the pulmonary artery is obstructed—such obstruction is almost always fatal from the sudden strain imposed on the right side of the heart. When the clot is smaller it passes further into the lung and obstructs one of the smaller pulmonary arteries and causes a cone-shaped hæmorrhagic infarction in the lung. When sudden death occurs after impaction of a small embolus in a tributary of the pulmonary artery, it is attributed to reflex constriction of the remainder of the pulmonary artery, if no other contributory factors can be found.

Ætiology. The primary clot does not necessarily form at the site of operation. Since many cases of embolism follow operations on the portal system, the thrombosis must obviously have been elsewhere. Post-mortem examination shows that in most instances the primary thrombosis has taken place in the large iliac veins, or in the hypogastric or femoral veins, or rarely in the inferior vena cava. The thrombosis is usually of "silent" type, and therefore escapes notice during life. In fatal cases the point from which a thrombus has become detached can be detected, and after its recovery from the pulmonary artery the thrombus may be refitted more or less accurately at its seat of origin. It is impossible to discover a lesion of the vessel wall, and usually there is no evidence of inflammatory reaction. The thrombus may be partly organized.

The most important factor in the causation of intravascular clotting is stasis of the blood current, and this is especially apt to occur in old age, debility, and anæmia. Post-operative shock and prolonged immobility of the lower part of the body during and after operation exert the same influence. Many local factors, especially in abdominal operations, may favour stasis in the large veins, such as prolonged pressure of packs and retractors, which, in addition, may injure the endothelial lining of vessels.

The importance of venous stasis in the causation of intravenous thrombosis is borne out by the infrequency with which pulmonary embolism follows operations on the upper part of the body, where the venous return is more active.

In addition to venous stasis, an important factor is the presence of an excessive amount of coagulant substances in the circulation. Such substances are set free in every wound and play a valuable part in the normal process of hæmostasis, but in extensive operations involving much injury to the tissues, it seems possible that excessive amounts reach the blood stream and thus favour intravascular clotting. In operations on the pelvic viscera the readiness with which the ferment may be absorbed locally into the large veins is obvious, and probably the proximity of large veins to these organs explains the frequency with which gynæcological operations are complicated by phlebitis and pulmonary embolism.

It is presumed that the intravascular clotting occurs at the time of operation, or at any rate, during the early post-operative period, when the maximum degree of venous stasis is present. The detachment of the thrombus from the surface of the veins is probably determined by sudden movement, such as coughing, or by sudden acceleration of the heart-beat following undue effort.

It has been suggested that infection plays an important part in causing the thrombosis, but there is little evidence in favour of this, except in so far as infection leads to or increases debility.

FAT EMBOLISM

Emboli of fat may lodge in the lung and sometimes the brain and other organs, and their effects may be fatal. This form of embolism sometimes follows fractures of long bones in adults and develops some three or more days after the accident. Less often it follows operations on bones (especially if they are rarefied), manipulation of joints or trivial injuries.

Fat emboli probably come from the site of injury, but the local condition which favours their entry into the circulation is not understood. There is some unconfirmed experimental evidence that the blood plasma-fat may be precipitated in the capillaries of the lung under certain conditions, especially if ether anaesthesia has disturbed the normal processes of emulsification of fat.

There are two types of fat embolism and they may be combined—the *pulmonic* (usually survived), in which the effects are due to widespread embolism in the terminal vessels; and the *systemic or cerebral*, in which emboli lodge in different viscera (usually harmlessly) and the brain, where they commonly lead to fatal ischæmic effects.

It is assumed that fat emboli reach the general circulation as a result of the increased circulatory tension in the lungs following upon obstruction of its vessels, or in some instances *viâ* a patent *foramen ovale*.

In fatal cases the appearance of the affected organs is characteristic. In the *lungs* there are areas of congestion and œdema and hæmorrhages beneath the pleura, and specific stains outline the fat droplets within the capillaries.¹ In the *brain* the emboli lodge chiefly in the grey matter and produce in its terminal vessels multiple foci of hæmorrhagic extravasation, likened to sprinkling of cayenne pepper.

More widespread embolism may be suggested by the discovery of fat droplets in the urine and petechial hæmorrhages in the skin.

AIR EMBOLISM

Air seldom enters a vein, but it may do so during operations in the neck or in the axilla or after stab wounds in these regions, and it has occurred during intravenous administration of fluids.

The entry of air into a wounded vein depends on the negative intravenous pressure which is caused by the suction power of the thorax and to a less extent by that of the heart. It is most likely to occur where collapse of a vein is hindered by stiffening of its wall due to disease or by adhesion to dense fasciæ. The entrance of air is recognized by a hissing sound in the wound, and this is followed by a churning sound in the chest caused by the air in the heart.

¹ Emboli of fat can be demonstrated within the lungs in about 14% of subjects after death.

Air embolism may occur at operations without apparent ill effect, for small amounts of air are held up in the pulmonary capillaries and are dissolved in the blood. Nevertheless, air embolism sometimes terminates fatally and at autopsy the right side of the heart is full of frothy blood. One or both lungs may have a bloodless appearance.

Cerebral air embolism sometimes occurs during paracentesis of the chest, and especially during the induction of artificial pneumothorax. Formerly the condition was confused with "pleural shock," which it resembles very closely. The embolism is due to the entry of air into one of the pulmonary veins as a result of puncture of the lung. The air may reach the pulmonary veins either through the needle used for artificial pneumothorax or from the alveoli of the lungs. It should be borne in mind that the pressure in the pulmonary veins is a negative one and that the air in the alveoli is at a slight positive pressure and may therefore be aspirated readily into a wounded vessel. The aspirated air passes through the left side of the heart to the systemic vessels, and a large proportion of it is directed to the carotid arteries and thence to the brain, and may cause loss of consciousness, blindness, paralysis or even death.

Experimental observations suggest that quantities of air over 20 c.c. introduced into the pulmonary veins may have a lethal effect.

SUPPURATION IN THE LUNG

Bronchiectasis

Many cases of bronchiectasis date back to childhood and owe their origin to bronchopneumonia or bronchitis following measles or whooping-cough. When the disease begins in adult life it is usually due to bronchopneumonia, often of influenzal origin. Either in children or adults bronchiectasis may follow the aspiration of a foreign body or other infective material into the lung. In a considerable number of cases no definite antecedent ætiological factor other than chronic infection of the nasal sinuses can be ascertained.

When bronchiectasis follows acute respiratory infection the changes in the lung can be traced to an acute interstitial inflammation going on to necrosis and suppuration, which destroys the bronchial wall (including the muscle, elastic tissue, and cartilage), invades adjacent alveoli and creates a cavity alongside the bronchus and in communication with it. The cavity may be cylindrical or saccular according to the extent of the destruction. In the healing process the walls of the cavities are converted into granulation tissue, which later becomes fibrous tissue, and are lined with bronchial epithelium derived from proliferation of such islets of mucosa as have not perished during the acute inflammatory process. The epithelium is of a varied type—cubical, stratified, or squamous.

In many cases of bronchiectasis (the so-called idiopathic) the pathogenesis is probably more insidious and the outcome of atelectasis resulting from bronchial obstruction by chronic inflammatory exudate or tuberculous hilar glands. The atelectasis is associated with an

increased negative pressure in the collapsed lung, which, if sustained, brings about dilatation of the more slender portions of the bronchial tree distal to the obstruction. Such anatomical possibilities have been supported by clinical and experimental observation.

In a bronchiectatic lung there is always a variable amount of interstitial fibrosis. It is greatest around the bronchi, but it is present also in the walls of the alveoli, and may sometimes extend to the surface of the lung. The fibrosis stiffens the walls of the bronchiectatic cavities and tends to keep them open, and hence the stagnation of secretions and persistence of infection which are such characteristic features of bronchiectasis. The destruction of muscle fibres and loss of the ciliated epithelium probably play a minor part in the retention of secretions. In all cases it is the severity of the superadded infection which determines the clinical manifestations of the disease. Thus in some it is latent (*dry bronchiectasis*), in others there is repeated (and sometimes fatal) hæmoptysis, and when there is gross infection, copious, often foul-smelling, sputum.

Bronchiectasis may be scattered through the whole lung, but more often is confined to a part or the whole of the arborescences of the lower lobe bronchus, with in addition sometimes the lingula portion of the lobe above. Occasionally the disease is bilateral from the onset, or it may become so later. On account of the diffuse fibrous infiltration and the loss of elasticity, the lung is smaller and more solid than normally, and its power of expansion is greatly diminished. Pleural adhesions are often present, especially at the base of the lung, but sometimes they are absent even in severe cases.

Bronchiectasis may be consistent with a state of moderately good health, but in many instances it is responsible for dyspnoea, cyanosis and chronic toxæmia. Exacerbations of the pulmonary infection may occur from time to time and may lead to a fatal issue. In a number of cases a metastatic cerebral abscess is responsible for death: sometimes the abscess is single, but quite frequently there are multiple abscesses in different parts of the brain.

Abscess of the Lung

This form of pulmonary suppuration differs from bronchiectasis, with which it is often confused, in that it begins in the parenchyma of the lung and involves the bronchi only secondarily. A pulmonary abscess is much less common than bronchiectasis. It may result from local or from distant infective processes, and, according to its mode of origin, the following varieties may be recognized.

(1) **Solitary Putrid Lung Abscess.** This is by far the commonest variety of abscess and is caused by anaerobic organisms. The source of the infection is the teeth, gums and tonsils: the infective material reaches the lung by aspiration (so-called bronchial embolus), and the part of the lung affected is probably determined by posture. The entry of infective material occurs when the cough reflex is abolished as in deep sleep, or while the subject is under the influence of narcotics or anæsthesia—as, for example, in dental extractions or during operations on the nose or pharynx.

The site of the abscess is surprisingly constant, situated mainly peripherally either in the posterior subapical axillary part of the upper lobe of the lung, or in the highest part of the lower lobe. The former is the commoner. It is therefore most evident in the axillary or the dorsal part of the chest. The disease may on occasion pursue a very abrupt course culminating in gangrene within a few days: in the majority the onset and progress are more gradual with a climax in the expectoration of quantities of evil-odoured thin pus.

If untreated the abscess is likely to become chronic because the drainage outlet is through small and swollen bronchi: indeed, total spontaneous healing occurs in little more than a fifth of cases, and its occurrence is not predictable in any one.

The outer wall of the abscess abuts on the pleura and is thin and is attached by moderately secure adhesions, usually sufficient to allow of drainage without contamination of the pleura.

Delayed drainage may result in rupture into the pleural cavity; attended sometimes by escape of air (tension pneumothorax), and aggravation of the disease.

(2) **Non-putrid Solitary Abscess.** This type is much less common. It is caused by aerobic streptococci, etc., which reach the lung by aspiration. It may occur too as a complication of pneumonia or of injury. The course of the disease is less acute than in a gangrenous abscess, so much so that it may sometimes simulate pulmonary tuberculosis or carcinoma. The outlook is more favourable than in other varieties of abscess as spontaneous resolution is quite usual.

(3) **Staphylococcal Abscess.** An abscess of this origin may develop in the lung in the course of staphylococcal pneumonia or as a late complication of influenzal pneumonia. It may be associated with similar infection elsewhere, *e.g.*, in joints. A staphylococcal abscess frequently involves the pleura secondarily. The disease though often fatal is sometimes survived.

(4) **Following Aspiration of Foreign Bodies.** Foreign bodies aspirated into the bronchi may after a variable interval lead to suppuration, especially bodies such as peas, nuts, etc., which undergo expansion and harbour infective material. Relatively sterile objects such as fragments of metal or beads may remain in a bronchus for months or even years without causing more than slight disturbance.

On account of the greater width of the right bronchus, an aspiration abscess is commoner in the right lung, and is most frequent in the lower lobe because of the more vertical direction of the hyperarterial bronchus. When a foreign body becomes impacted in a bronchus the mucous membrane surrounding it becomes swollen, so that obstruction of the bronchus may become complete. The lung beyond it becomes atelectatic. Secretion of mucus from the bronchus is increased at the site of impaction, and ulceration and infection generally occur. The infection spreads through the bronchi into the lung parenchyma, and may give rise to single or multiple abscesses. The abscess is generally multilocular and has the combined features of bronchiectasis and a chronic lung abscess.

(5) **Pyæmic.** In infected surgical wounds, septic thrombophlebitis,

acute osteomyelitis, etc., infected emboli may be carried by the veins to the lungs, where they give rise to septic infarcts and abscesses. The abscesses are usually small and multiple and situated at the periphery of the lungs. The disease is generally fatal.

(6) **Associated with Tumours, etc.** The ulcerated surface of a carcinoma is very liable to infection. Suppuration, aggravated by necrosis of the tumour, may result in a large abscess. At least 25% of pulmonary cancers are finally complicated by suppuration.

Less common causes of a lung abscess are (a) lodgment of missiles or of infective material conveyed by them, (b) extension of a subphrenic abscess, and (c) superadded infection of a congenital or hydatid cyst in the lung.

Morbid Anatomy and Course of the Disease. Abscesses of the lung may be single or multiple, and one or both lungs may be affected. The pathological features are conditioned by the underlying cause.

The abscess is usually single and of large size, and is usually situated at the periphery of the affected lobe. At first the affected portion of lung is consolidated, œdematous and necrotic. Suppuration and abscess formation follow or actual gangrene may occur. The abscess, which is not at first definitely circumscribed, is surrounded by congested and intensely inflamed lung tissue. It is usually more or less spherical, and there may be smaller abscesses communicating with it. After a variable time the abscess usually burrows into one or more bronchi or if it is near the surface of the lung it may rupture into the pleural cavity. When it ruptures into a bronchus a large quantity of thin pus is expectorated, and this may be repeated at intervals for a long time. The pus is of light green or yellow colour, occasionally altered by blood, and is usually very fœtid.

The interior of a lung abscess varies in appearance according to its duration and the extent to which necrosis has occurred. In an acute lung abscess the walls are soft and flexible, and are covered with shreds of sloughing tissue. One or more bronchi communicate with it and serve as channels for drainage. Later the wall of the abscess may assume a dull granular appearance or become smooth and fibrous.

The cavity of an acute lung abscess may become obliterated by expansion of the lung around it and by fibrosis, and may be completely healed. Healing may be defective if drainage of the abscess into the bronchi is insufficient. When drainage of an abscess is inadequate its wall tends to become rigid from fibrosis, and the abscess becomes chronic, and later epithelium may regenerate within its walls. In addition, a variable degree of bronchiectasis develops as a result of infection and disorganization of bronchial walls and traction of scar tissue.

Pathological Sequelæ of a Lung Abscess. One of the commonest sequelæ of a pulmonary abscess is *cerebral abscess* (most often in the left hemisphere), due to an embolus formed by the dislodgment of a thrombus from one of the pulmonary veins. This catastrophe can occur during either the acute or the chronic stage of the abscess, and occasionally follows operative interference. *Hæmorrhage* may result from ulceration into one of the pulmonary vessels in the wall of the lung

abscess and be fatal. *Amyloid disease* is a sequel of long-standing lung abscess.

PULMONARY TUBERCULOSIS FROM A SURGICAL STANDPOINT

During recent years surgical measures have been extended to the treatment of tuberculosis of the lungs. In the lungs as in other structures the seat of tuberculous infection, healing is favoured if sustained physiological rest can be procured; and for that purpose (in selected cases) there are now available a variety of methods known collectively as "collapse therapy." The specific effect of all forms of collapse therapy is the reduction of lung volume regionally or generally, with resulting diminution of tension (atmospheric and general) so that reparative processes may not be inhibited or, if already present, can proceed unhampered. The choice of method is conditional upon the particular pathological features present in the diseased lung and pleura, and especially upon whether or not the lung is adherent to the parietes. Many of the operations, such as intrapleural division of adhesions and apicolysis, are employed for the obliteration of persisting cavities which may be a source of hæmorrhage or reinfection of the lung.

Only a limited proportion of cases is suitable for surgical treatment, because the methods are applicable chiefly to those in which the disease is confined to one lung.

There are two main types of pulmonary tuberculosis: (1) chronic fibro-cavernous or "productive," and (2) relatively acute pneumonic, caseous, or "exudative." It is with the less acute and chronic types that surgery is especially concerned.

In the chronic fibroid type there is a definite tendency towards fibrous encapsulation of the tuberculous lesions. The disease is often limited to the subapical region of the upper lobe and to the upper part of the lower lobe. Cavities communicating with bronchi are often present, and both cavities and other lesions are surrounded by dense zones of fibrous tissue. This fibrous induration leads to shrinkage of the lung, and, as a result, to retraction of the chest wall and deflection of the mediastinal septum towards the diseased side (*see* Fig. 144). In some cases the shrinkage is sufficient to obliterate the cavities and to permit healing of the disease, but more often the shrinkage is interfered with by the fixity of the chest wall, and when the limits of fibrous tissue encapsulation and contraction are reached the healing processes cease. It is then that operations designed to paralyse the diaphragm, or to mobilize the rigid chest wall, may be carried out, in order to relax the scar tissue and permit it to shrink tightly round the tubercles and cavities.

In the acute type of disease, which is commonest in young adults, there is at first little fibrosis. The disease tends to advance widely in the lung and to culminate in caseation and cavity formation. It is in this type that immobilization of the lung by artificial pneumothorax is calculated to produce local conditions favourable for resolution and fibrosis.

Therapeutic collapse of the lung not only gives rest and immobility to the diseased lung, but also, in combination with the ensuing shrinkage, empties the lung of its accumulated products, the evidence of which is the immediate increase of sputum followed by diminution in the amount. Cavities whose walls are not very stiff may be reduced to mere clefts, and their ulcerated walls may heal. The toxic products have not the same chance of dissemination owing to the lymph stasis that follows the pulmonary collapse; the benefit of this is shown by

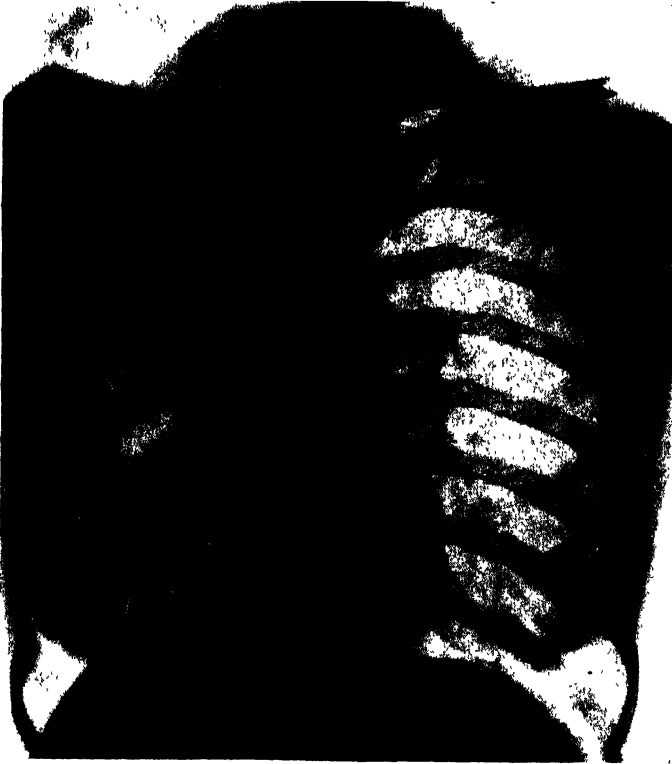


FIG. 144. Radiogram of chronic fibroid phthisis of the right lung, in a female aged twenty-four years. The trachea and the heart are deflected towards the diseased side.

the improvement in the general condition of the patient. The lymph stasis also prevents the further dissemination of bacilli.

Pleuro-pulmonary Adhesions. When artificial pneumothorax has been instituted adhesions of varying number and degree between the lung and the parietal pleura may become obvious. The adhesion is the result of former pleurisy: it may extend over a broad surface (symphysis) or be quite circumscribed though at multiple points, especially over the upper lobe of the lung. When the pneumothorax has been present for some time they may become attenuated: it is in such circumstances that division of the adhesions intrapleurally is attempted. It is important to appreciate that the stouter and more

sessile adhesions often contain lung tissue or even prolongations of underlying cavities which are liable to injury. Likewise adhesions of long standing may contain tissues drawn inwards from the extrapleural layers: these tissues are often vascular and when divided may be responsible for hæmorrhage.

CONGENITAL CYSTIC DISEASE OF THE LUNG

This condition has attracted increasing interest during recent years, no doubt on account of its frequent discovery on radiographic examination of the lungs. The disease assumes two main forms: (1) a solitary or multiple large cysts, containing fluid or air; and (2) diffuse cystic disease.

The first variety has usually been met with in childhood. The cyst may attain an enormous size and fill the entire pleural sac of one side (the so-called balloon cyst). Such a cyst is at first probably of small size and may contain fluid whose escape into a bronchus allows a gradual air distension of its walls so that finally the healthy lung tissue is condensed around it. In the same way multiple cysts may evacuate their contents and become inflated with air, and either form multiple air-containing cysts or, if the dividing walls rupture, a single trabeculated cyst. The lining membrane is usually columnar or cubical epithelium, and the walls contain unstriped muscle, elastic and fibrous tissue and sometimes cartilage. The appearances may be profoundly altered by infection.

A large cyst when uncomplicated may cause only slight symptoms, such as cyanosis and dyspnoea. But if the air-pressure within the cyst becomes excessive (due to a valvular communication with a bronchus), severe respiratory distress or fatal asphyxia may result. In a number of instances rupture of the cyst into the pleural cavity occurs.

Diffuse cystic disease is more common. It may involve a part or the entire lung, and is often bilateral. The cysts may be mere clefts, but are more often rounded, and vary in size from a pea to larger than a golf ball. Many of the cysts communicate with the finer bronchi. The bronchi are not dilated. In an X-ray film the appearance is very characteristic and merits the title of "honey-comb" or "soap-bubble" lung. Superadded infection is common, and creates features comparable clinically to bronchiectasis.

The developmental nature of cystic disease of the lung is suggested by its occurrence in infancy and by the epithelial character of the lining membrane of the cysts. It is assumed that in most cases the cysts are developed as diverticula from the smaller bronchi or from the atrial sacs.

Attempts have been made to establish a relationship between cystic disease and bronchiectasis, but the pathological evidence suggests they are independent entities, although the condition of bronchiolectasis found in infancy may represent a developmental abnormality allied to cystic disease.

TUMOURS OF THE LUNG

Simple tumours of the lung are very rare. Myoma, fibroma, chondroma and angioma have been described. They are usually

discovered accidentally and seldom produce pathological effects.

A simple adenoma commonly occurs in one of the main bronchi and may reach a large size. It may be responsible for hæmoptysis, atelectasis or bronchiectasis with suppuration (see Fig. 145). It affects men and women equally, and occurs at an earlier age (twenty-five to forty years) than lung cancer.

A bronchial adenoma is sometimes pedunculated and is then accessible to removal from within the bronchus. In other instances the tumour projects into the bronchus and its deeper part expands into the adjacent lung, the resulting tumour assuming an hour-glass form.

Microscopically bronchial adenomata show considerable individual variation in structure. Some show a glandular pattern with tubules and acini. In others there is less differentiation and the cells are in solid acini or irregular masses. The cells are, however, uniform in size and are cuboidal with a large nucleus and scanty cytoplasm.

A bronchial adenoma originates from the secretory ducts of the bronchial mucous glands. Its histological variations are very similar in form and nature to those present in salivary gland tumours and the two types of tumour are held to be akin in origin and behaviour.



FIG. 145. Adenoma of the bronchus. The growth has obstructed the lower lobe bronchus which in consequence is greatly dilated.

Primary Cancer of the Lung

Statistics based on post-mortem records suggest that the incidence of cancer of the lung

has increased during the past ten or fifteen years, and that the increase is a real one and is independent of improvements in clinical and pathological diagnosis. The cause of the increase has not been fully accounted for.

Many substances have been suggested as predisposing factors in the development of lung cancer, such as silica, petrol fumes, tar from road dust, etc., but proof is lacking that they are responsible. The only known association between exposure to dust and the development of bronchial carcinoma is that of the Schneeberg miners, and in

them the radioactive properties of the dust are now held responsible. By some, chronic bacterial infections are regarded as a potential predisposing cause, probably as a result of the epithelial metaplasia to which they may give rise in the bronchi. Active tuberculosis and carcinoma may coexist in the lung, but the occurrence is purely accidental.

Cancer of the lung occurs most often between the ages of forty and sixty years, and is much more common in men than women (4:1).

Morbid Anatomy and Histology.

In the majority of cases cancer in the lung begins in the mucous membrane of the main or secondary bronchi and only seldom more peripherally. The new growth may start in the cylindrical epithelium of the bronchial mucosa or in the basal epithelium. The histological appearances are very diverse, and variations within individual tumours are not uncommon. The following are the



FIG. 146. Lipiodol-radiogram of early bronchial carcinoma. The left lung field is opaque and lipiodol fills the left bronchus above the level of the obstruction. The right lower bronchial tree is outlined normally. Lipiodol in the œsophagus is seen in the lower portion of the picture.

(By courtesy of Dr Scott Park.)

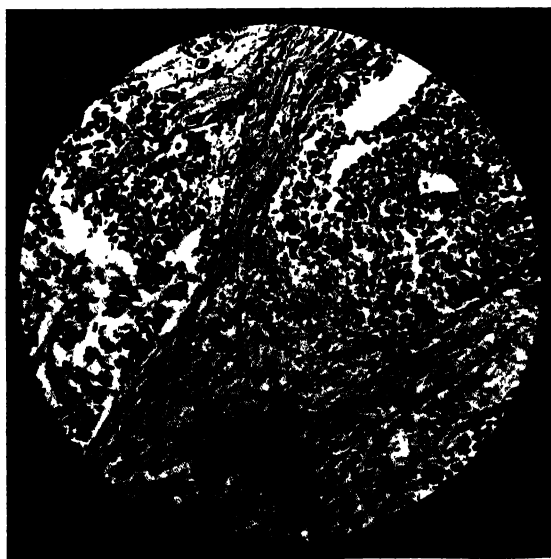


FIG. 147. Carcinoma of bronchus of "oat-cell" type. $\times 150$.

(By courtesy of Professor J. W. S. Blacklock.)

common types: (1) columnar-cell carcinoma, (2) "oat-cell" carcinoma, (3) squamous-cell carcinoma. Tumours of the first type are composed of columnar cells, which are differentiated to a moderate degree and are arranged, for the most part, in an irregular acinar or papillary formation. Tumours of the second, the commonest type — the "oat-cell" carcinoma — are composed of undifferentiated cells of small size,

rounded or of oat-seed shape, with deep-staining nuclei and scanty cytoplasm. The majority of the cells are arranged irregularly, with a very scanty fibrous tissue stroma and little tendency towards glandular structure.

Tumours of this type were regarded formerly as mediastinal sarcomata, but careful examination generally affords evidence of an epithelial origin. Tumours of the third type are composed mainly of irregularly arranged squamous cells, and to some extent they resemble squamous-cell carcinoma in other situations, though cell nests or keratinization are seldom highly developed.

The commonest starting point of a bronchial carcinoma is at or about the point where the main bronchus gives off its branches. It usually spreads both up and down the bronchial wall and also round it and may finally occlude the lumen of the bronchi. When examined by bronchoscopy or at autopsy the growth is often small, greyish white, granular and slightly nodular on the surface. It may be pedunculated and may occlude the lumen of the bronchus. It may spread in the submucosa over a considerable area without ulceration, and it may extend directly to the trachea or even to the opposite bronchus. The most important effect of a bronchial carcinoma is production of stenosis of the larger



FIG. 148. Bronchial carcinoma of the left lung. The patient was a male aged fifty-four. The disease was complicated by suppuration in the lung and empyema.

(Department of Pathology, University of Edinburgh.)

bronchi, and therefore atelectasis and bronchiectasis are common secondary results.

A bronchial carcinoma tends to infiltrate the parenchyma of the lung till a lobe or even the entire lung may be converted into a solid

mass of firm texture and yellowish-white colour. Degeneration within the tumour, sometimes attended by suppuration, is a common event. Sometimes spread by the peribronchial lymph vessels is an outstanding feature, and may lead to extensive involvement of the pleura, often with a large effusion of clear or sanious fluid due to widespread lymph vascular obstruction. The tracheo-bronchial lymph glands and the hilum of the lung are invaded at an early stage, and it sometimes happens that the bronchial growth remains very small and localized, while the secondary growths are large and give rise to pressure on large vessels, and on the trachea. Such secondary growths may be mistaken for mediastinal sarcoma. Rarely the lymph glands at the root of the neck may be infiltrated, especially in carcinoma of the upper lobe of the lung. Occasionally a small bronchial tumour leads to atelectasis so that the lung is no larger than a fist and the pleural cavity becomes the seat of a very large effusion.

In a few instances a carcinoma begins in a fine or tertiary bronchus and tends to grow peripherally rather than towards the hilum. This type often assumes and maintains a spherical form in the substance of the lung. It is of slow growth and metastasizes at a late stage or not at all.

The pathological effects of a bronchial carcinoma may be very few, but in about 25% secondary bronchiectasis occurs. Ulceration of the surface of the growth leads to excessive mucoid or sanious discharge, and sometimes tumour cells can be detected in the sputum.

Apart from the neighbouring lymph glands the liver (80%) is the commonest site of secondary growths. Metastases are common also in the kidneys (15.9%), the suprarenal glands (9.7%), and the brain (9.5%). They have been observed also in bones (10%), especially in the vertebræ and long bones. A cerebral metastasis may give rise to confusion in diagnosis and errors in treatment if the primary growth is symptomless.

In the majority of cases the onset of signs or symptoms is very insidious, and the tumour is often far advanced before they develop. The following are the common ways in which the disease may manifest itself: (1) by hæmoptysis and cough, (2) by pleurisy, with or without effusion, (3) by pulmonary suppuration, (4) by increasing debility, dyspnœa, and emaciation.

DISEASES OF THE MEDIASTINUM

Acute Septic Mediastinitis

The areolar tissue of the mediastinal septum is of loose texture, and consequently any infective process tends to spread widely in it, and, as it is richly supplied with lymph vessels, toxic absorption generally has serious results.

Acute mediastinitis most often takes the form of diffuse cellulitis, and the anterior mediastinum is most commonly affected. The cellulitis may on occasions result in the formation of an abscess, but more often its effects are lethal before suppuration begins.

Mediastinitis may arise (1) as a complication of cellulitis of the neck, *e.g.*, Ludwig's angina, (2) following operations on the larynx, pharynx, trachea or œsophagus, (3) as a result of perforation of the pharynx or œsophagus by a foreign body, (4) from leakage of infection from an ulcerating carcinoma of the pharynx or œsophagus, and (5) rarely, secondary to osteomyelitis of a thoracic vertebra.

In mediastinitis, the tissues are very swollen, œdematous and congested. Areas of necrotic fat, often of a greenish colour, are present, and there may be small abscesses scattered through the inflamed tissues. When perforation of a hollow viscus has been responsible for the infection, gas may infiltrate the inflamed tissues, which are then extremely malodorous. The lymph glands are enlarged and sometimes softened, and the fibrous pericardium may share in the inflammation.

When an abscess forms in the anterior mediastinum it may extend upwards and produce œdema and redness of the skin at the root of the neck, and it may point in the suprasternal notch or accompany the subclavian vessels into the posterior triangle, or burrow through an intercostal space at the margin of the sternum. An abscess in the superior and posterior mediastina may rupture into the trachea, œsophagus or pleural cavity.

Emphysema of the mediastinum is a rare sequel of crushing injuries of the thorax. The air may escape from the trachea, the bronchi or the lungs. At each inspiration more and more air is forced into the mediastinum, and it may finally compress the large veins, especially those at the lung root.

Cysts of the Mediastinum

Cysts of the mediastinum are comparatively rare, but they are of interest in respect that they are amenable to surgical treatment.

The commonest are dermoid cysts and teratomatous cysts: generically they are alike. They may arise in the posterior mediastinum, but usually they begin in the superior mediastinum behind the manubrium (retrosternal). Commonly, as the cyst grows, it bulges towards the pleural cavity on one or both sides (mediastino-thoracic), or it may reach the root of the neck (mediastino-cervical). The origin of the cyst is probably not the same in all cases. It is believed (though not proved) that a mediastinal dermoid arises from the downward displacement of remnants of the 3rd and 4th branchial arches. Less often it may arise from inclusion of the epidermis, for defects of the sternum may coexist.

In structure a mediastinal dermoid does not differ from those elsewhere. It may be entirely cystic or in parts solid. Sebaceous material, fat, hair, and teeth are common constituents of the tumour.

Dermoid and teratomatous cysts vary in size from a golf ball to a foetal head. Their growth is slow, and since the cyst extends laterally it acquires a covering of mediastinal pleura, and it may insinuate itself between the lobes of a lung and thus simulate an intrapulmonary tumour.

Mediastinal cysts are very liable to infection, especially after pneumonia or influenza or one of the zymotic diseases. Suppuration

within the cyst causes a rapid increase in its size, and the cyst may perforate the trachea or bronchi, with the result that sebaceous material or hairs are expectorated. Empyema may occur or the pus may penetrate the chest wall or ascend to the neck. Inflammation in the cyst renders it very adherent to the lung, pleura and large vessels, and adds to the difficulty of its removal. Malignant degeneration of a teratoma and dermoid is well known.

A much rarer cyst of the mediastinum is one known as a bronchogenic or tracheo-bronchial cyst. It is usually in contact with the trachea or main bronchi and may reach considerable size. The cyst wall differs from that of a dermoid in that it is very thin and lacks hair-forming epithelium and sebaceous glands. The epithelium is of a



FIG. 149. Tracheo-bronchial cyst. The cyst is lined by ciliated epithelium. Its walls contain areas of cartilage.

cylindrical type, and may be ciliated. Numerous glands and bundles of plain muscle fibres or cartilage may lie deep to the epithelium.

Such a cyst is of vestigial origin, from extrusions of the developing trachea or bronchi.

Primary Tumours of the Mediastinum

Malignant tumours of the mediastinum include thymoma (p. 360), lymphosarcoma and neuroblastoma.

Simple tumours include lipoma, fibroma, chondroma, and ganglioneuroma.

Rarely a mediastinal tumour extends through an intervertebral foramen into the spinal canal, assuming an hour-glass shape; similarly a tumour arising within the spinal canal may extend into the mediastinum. Hæmorrhage or degeneration within the spinal portion may result in paraplegia.



FIG. 150. Ganglioneuroma of the mediastinum. The tumour has been split : note the area of hæmorrhage and multiple foci of calcification.

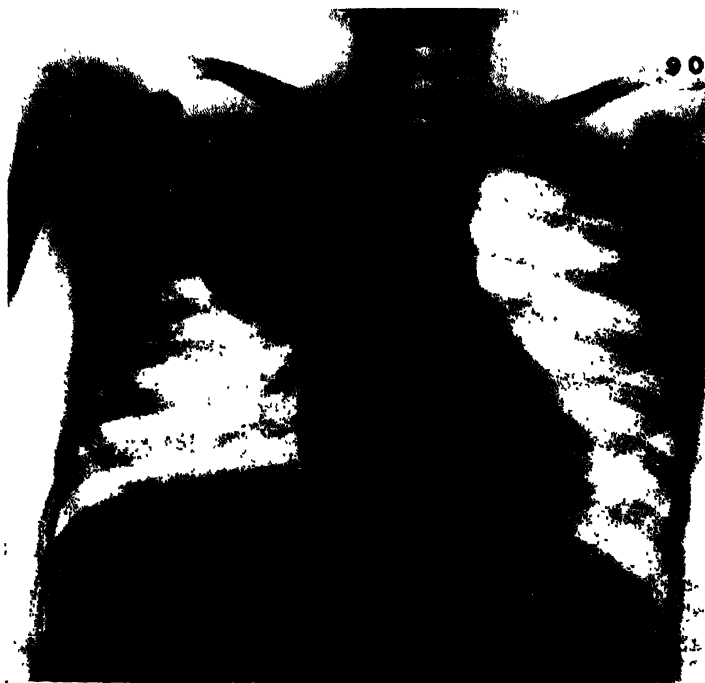


FIG. 151. Radiogram of a ganglioneuroma of the mediastinum which extended into the right side of the chest. The tumour occurred in a female nine years of age, and had caused dyspnoea, hæmoptysis, and paroxysmal coughing. A prominence in the back corresponded to a partially dislocated third rib.

Lastly there is the rare "Superior sulcus tumour." Under this title is described a localized tumour which arises extrapleurally at the thoracic inlet in front of the first and second ribs and the transverse processes of the respective vertebræ. The tumour is usually sharply defined and spherical, and when first observed is seldom larger than a golf ball. From its proximity to important nerve trunks it gives rise at an early stage to pressure on the cervico-dorsal sympathetic and the lower trunk of the brachial plexus; and a Horner's syndrome, severe brachial neuritis and paralysis of the muscles of the hand are the common effects. Superficial erosion of the ribs and vertebræ is often present.

The tumour is hard and fixed and of grey or yellow colour. Microscopically, it is a squamous cell carcinoma, probably of branchiogenetic origin.

Pathological Effects of Mediastinal Tumours. The effects of a mediastinal tumour are mainly due to pressure on neighbouring structures, although in the case of cystic tumours infection may lead to additional features. It is unusual for any disturbance to be noticeable before the age of puberty, and symptoms are sometimes deferred until the third or fourth decade. Pressure on the trachea is one of the most important effects. It tends to appear after some respiratory infection, and results in cough and often in dyspnoea or in stridor. In a few cases hæmoptysis occurs.

Pressure on the large venous trunks at the thoracic inlet may lead to dilatation of the superficial veins of the thorax or in the neck. Cyanosis may be present at a later stage. Pressure on the intercostal nerves may lead to pain or hyperæsthesia, and there may be pupillary changes from pressure on the sympathetic nerves. When large, the tumour may cause localized bulging of the chest wall either in front or behind.

Intrathoracic Goitre

Any large goitre may have a prolongation of its inferior extremity behind the sternum into the superior mediastinum. Such extension is favoured by gravity and the suction of inspiration. The resistance offered above and in front by the infrahyoid muscles makes this line of descent the path of least resistance.

In a true intrathoracic goitre, however, there is no obvious swelling of the thyroid gland in the neck, and the thyroid enlargement is entirely within the thoracic cavity.

An intrathoracic goitre is due most often to a colloid adenoma attached to the inferior extremity of the gland, especially on the left side. Rarely the condition is bilateral. The adenoma may be soft or hard, but frequently it is partly or wholly cystic, and calcification sometimes occurs in the wall of the cyst. The tumour retains its investment of pretracheal fascia, and its arterial supply resembles that of a cervical goitre and comes from the neck. In many cases the intrathoracic goitre is connected with the parent gland by an isthmus of thyroid tissue, but in old-standing cases the connexion may be fibrous.

As the goitre is enclosed in the pretracheal fascia it moves with the

rest of the thyroid gland on deglutition, and movement, when observed radiographically, is of great assistance in diagnosis. In the superior mediastinum an intrathoracic goitre rests on the parietal pleuræ of one or both sides, which form a bed for it. The innominate veins are situated deep to the tumour and may be displaced and compressed by it. Toxic hyperthyroidism in association with an intrathoracic goitre is extremely rare.

The Effects of an Intrathoracic Goitre. (1) **On the Trachea.** One of the most important effects produced by an intrathoracic goitre is compression and deviation of the trachea. The trachea becomes stretched over the anterior or lateral surface of the tumour, and as a result its lumen is often reduced to a very narrow channel. The tracheal displacement may be confirmed by inspecting or palpating the neck, and the larynx may participate in the deviation. A radiogram demonstrates the displacement and deformity. Cough, stridor, and dyspnœa, which are common features of an intrathoracic goitre, are explained by the implication of the trachea.

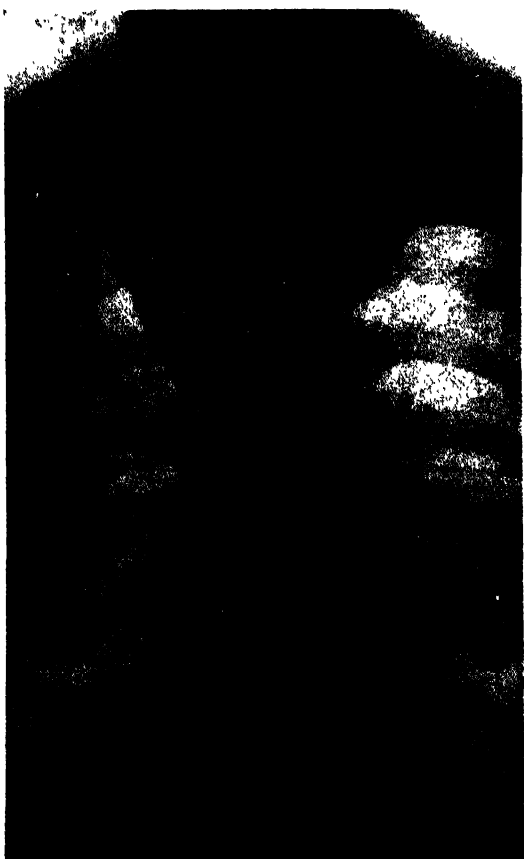


FIG. 152. Radiogram showing retrosternal goitre. The trachea, faintly outlined, is deflected to the left.

(2) **On the Large Vessels of the Thoracic Inlet.** Obstruction to the venous return from the neck and upper limbs is manifest by engorgement of the superficial vessels of the neck and front of the thorax. It is responsible for profuse bleeding when operation is undertaken. Sometimes the face and lips and the upper limbs show a trace of cyanosis. Œdema of the upper limbs has been observed. The large arteries are seldom compressed.

(3) **On the Recurrent Laryngeal Nerve.** Occasionally one of the recurrent laryngeal nerves, especially the left, may show some degree of paralysis.

(4) **On the Œsophagus.** It is very exceptional for the Œsophagus to be compressed, and therefore dysphagia is a rare symptom.

From the surgical

point of view an intrathoracic goitre presents difficulties which are not present in the treatment of a normally placed goitre. The engorgement of even the smallest superficial vessels is responsible for excessive bleeding. The proximity of the goitre to the large veins of the thoracic inlet may be responsible for serious bleeding, but this can be prevented if care is taken in operating to keep within the fascial capsule of the gland; likewise, if the enucleation of the goitre be conducted in this plane there is less risk of opening the pleura. Delivery of the goitre is facilitated by traction on the affected lobe or its connecting pedicle; but when it is very bulky it may be impossible to release it from the mediastinum unless it be diminished in size by excavation of its contents if that has not already occurred accidentally. Division of the sternum, to increase the diameter of the thoracic inlet, should seldom be necessary.

Diseases of the Thymus Gland

The thymus is of entodermal origin and develops as a paired tubular outgrowth from the third and fourth branchial clefts. The outgrowths lose their connexion with the clefts and fuse in the middle line, and the tubular structure later becomes folded on itself to form a solid bilobed organ. While the thymus is still connected to the primitive pharynx, outgrowths, which appear as aggregations of lymphoid tissue, arise at intervals on the superficial aspect of the tubules, and ultimately form the cortex of the thymic lobules. The origin of the lymphocytes is uncertain, but it is probable that they arise from the entodermal cells of the primitive tubules.

Apart from certain pathological conditions the thymus is found in its full development only in the foetus and in childhood. In adolescence the thymus undergoes retrogressive changes, and in adult life very little glandular tissue remains, as most of the epithelial elements are replaced by adipose tissue.

The fully developed thymus is composed of a mass of lobules separated from one another by strands of fibrous tissue which contain the blood vessels. Each lobule consists of a cortex and a medulla, the cells of which are quite different. The cortical portion resembles lymphoid tissue, but it contains no germ centres. Amongst these lymphoid cells, which are known as thymocytes, numerous indications of mitosis may be noted, and, in addition, there are a few large granular cells whose nature is not known. The medulla is of less compact structure, and is composed of a reticulum of large, translucent branched cells which are massed together in places. Most characteristic of the medulla are the concentric corpuscles (of Hassall), which consist of flattened epithelial cells arranged concentrically around one or more cells that have undergone hyaline degeneration, an arrangement which may lend an appearance of acinus formation.

Lymph vessels have not been demonstrated inside the lobules of the thymus, but lymph channels containing lymphocytes can be seen in the interstitial fibrous tissue of the gland. Williamson and Pearce at one time suggested that the thyroid and the thymus are closely related, both morphologically and functionally, and that the two organs

are connected by lymph channels, whereby part of the secretion of the thyroid gland is conveyed to the thymus.

Aberrant thymic tissue has been found within the thyroid and parathyroid glands and also in the areolar tissue of the neck. Parathyroid tissue also has been identified in the thymus, an association which, on a developmental basis, is understandable.

Enlargement of the Thymus

In early childhood the thymus may grow to abnormal size and lead to pressure on the trachea which may produce or terminate in stridor or asphyxia. In such cases it

is evident that the thymus shares in a generalized hyperplasia of the lymph glands of the neck or of the mediastinum and also the palatine, pharyngeal, and lingual tonsils. To this generalized overgrowth of the lymphoid tissues of the body the name *status thymolymphaticus* has been assigned.

In some pathological conditions in adult life the thymus may undergo hyperplasia and resume its infantile appearances. This is most commonly found in toxic goitre, but its significance is not understood; the thymic enlargement is not invariably present nor is it ever excessive, and the appearance of the gland is not very different from that of the normal organ of childhood. Williamson and Pearce emphasized the association of thymic hyperplasia and toxic goitre and regard it *inter alia* as evidence of the functional unity of the thyroid and thymus. They believed that the thymus had a detoxi-



FIG. 153. An encapsuled carcinoma of the thymus gland from a man aged fifty-nine years. The tumour had caused dysphagia. Death was due to purulent bronchitis. There were no metastases.

(Photograph lent by Dr. Stuart McDonald.)

ating action on a supposed lymph-borne secretion from the thyroid. In the belief that the thymus is closely associated with thyrotoxicosis, surgeons have removed the gland in the treatment of that disease, and, in some cases, with apparent benefit.

The thymus is said to be enlarged in about 50% of cases of myasthenia. The enlargement is usually due to epithelial hyperplasia, but it may be the result of a cyst, a simple or a malignant tumour. There is no characteristic histological feature of the hyperplasia of the gland

found in myasthenia, although a notable reduction in the number of Hassall's corpuscles has been described.

The relationship between the functional defect in myasthenia gravis and thymic hyperplasia has not been explained. It has been suggested that the thymus releases an inhibitor substance into the circulation which reduces muscle activity. Removal of the thymus has brought about striking relief in some instances.

The thymus may be enlarged in rickets, Addison's disease, and leukæmia.

Cysts of the Thymus

Cysts of the thymus are rare. They may arise as a result of persistence of its embryonic epithelial ducts. Most often the cystic change is of a lymphangiomatous character and may lead to very great enlargement.

Cyst formation may occur in outlying islets of thymic tissue in the neck, and cysts of the thyroid gland, containing lymphocytes and Hassall's corpuscles in its walls, have been recorded. It has been suggested that the cystic hygroma of the neck may originate in aberrant thymic tissue.

Tumours of the Thymus

There are two chief types of thymic tumour : (1) lymphosarcoma, or malignant thymoma, and (2) thymic carcinoma. Thymic sarcoma,

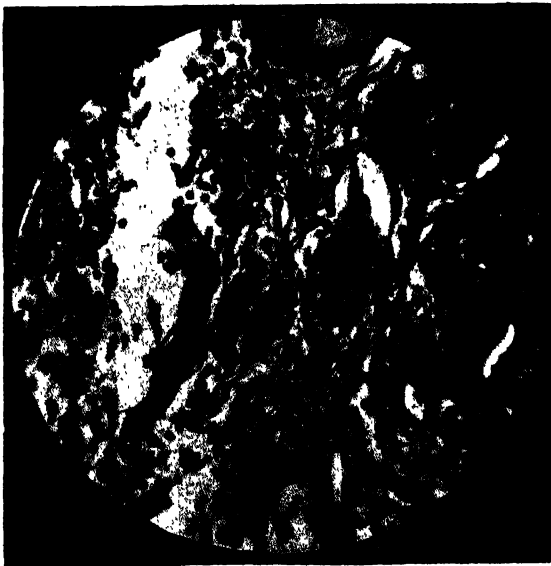


FIG. 154. Photomicrograph of thymic tumour depicted in Fig. 153, showing reticulum cells and lymphocytes.

usually of a spindle-celled type, has been described, but there are strong grounds for concluding that all the co-called spindle-cell tumours are histological variations of thymoma.

(1) **The malignant thymoma** is the commoner. It is usually a firm, lobulated tumour, which on section presents a yellow colour, often with areas of necrosis or hæmorrhage. The tumour is sometimes encapsuled, but as a rule it infiltrates the pleura, lung, pericardium, trachea or great vessels. It occupies the anterior mediastinum and may extend into the neck, or it may bulge or perforate the sternum. Secondary deposits may be found in the cervical, axillary or bronchial glands, and in the liver, spleen, pancreas and the bones. The tumour grows rapidly and compresses or invades the trachea. Eosinophilia is often a prominent feature.

Histologically, these tumours do not conform to a standard pattern. Some specimens may have an appearance like lymphadenoma, and in

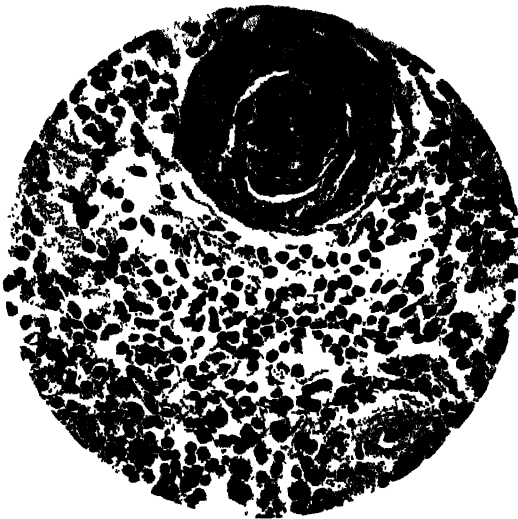


FIG. 155. Malignant thymoma, showing malignant lymphocytic tissue and a concentric laminated body.

(Laboratory of Royal College of Physicians of Edinburgh.)

them reticular cells predominate. Others have the appearance of a lymphosarcoma, from which they can be distinguished only with difficulty. The tumours are usually very radio-sensitive.

(2) **Thymic Carcinoma.** This is a less common tumour and exerts the same effects. It has been noted that its infiltrative powers are less obvious than is usual with carcinomatous growths in other regions. Microscopic examination of a typical example shows coherent sheets, cords, and columns of large, flat, or polyhedral epithelial cells lying in dense fibrous tissue. Cornification is absent, but concentric layers of flat cells may form structures resembling concentric corpuscles. In other cases the squamous characters are less evident, and the cells are chiefly cubical and form alveoli. In many cases both epithelium and round cells share in the tumour, which accounts for the designations *carcino-sarcoma* or *adeno-sarcoma*.

Carcinoma of the thymus has been observed in association with cases of over-activity of the suprarenal gland.

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CHAPTER XVII

DISEASES OF THE BREAST

STRUCTURE OF THE BREAST

THE epithelium of the breast, the lining membrane of its ducts and acini, is derived from the epidermis on the ventral aspect of the fœtus, and the breast may be regarded as a collection of greatly modified sweat glands. The first indication of the developing breast is to be found in the second month of intra-uterine life. At this period the ducts, twelve to twenty in number, appear on the deep aspect of the epidermis and extend as solid cords into the superficial fascia, from which they derive a supporting framework. The ducts become canalized, branch repeatedly and form abundant lobules, which extend into the surrounding fibrous tissue. From their blind extremities the acini develop. The acini are scanty and ill-developed until puberty, after which they show a remarkable faculty for periodic proliferation and retrogression.

The fully developed breast consists of a number of lobules, each somewhat pyramidal in shape and supported by a framework of tough fibrous tissue. On the superficial aspect, this framework is attached to the deep surface of the skin by the suspensory ligaments (ligaments of Cooper).

The ducts, deep to their orifices, expand just below the nipple to form ampullæ, which serve as reservoirs for milk. At the nipple the ducts are lined by squamous epithelium continuous with the skin, and as they are narrow they are liable to be occluded, either by periductal fibrosis or by epithelial *débris* in the lumen. Below the nipple the ducts are lined by a double layer of columnar or cubical epithelium, supported by connective tissue, in which both elastic tissue and plain muscle fibres may be recognized. As the terminal ducts are approached the elastic tissue and muscle fibres gradually diminish in number, and the acini, which in the virgin breast are scanty and small, are lined merely with epithelial cells and a basement membrane. Ducts and acini lie embedded in an abundance of areolar tissue, which is in turn bounded by the tougher supporting framework of the gland. The delicate tissue immediately surrounding the acini fulfils an important rôle, for during pregnancy and lactation it provides a ready "accommodation space" for the immense proliferation of secretory cells then required.

Physiological Changes in the Breast. In infancy and childhood the breast remains undeveloped, and consists principally of the larger ducts embedded in fibrous tissue. Acini are scanty, and those present are of small size. In the male this state persists throughout life, but in the female the gland undergoes remarkable changes in preparation for its functional activity during the reproductive period.

The first of these changes usually begins at puberty. At this time

the breasts increase in size slightly, the ducts branch and rebranch, and from their extremities alveoli of secretory cells bud out. Occasionally this physiological hyperplasia may be exaggerated, and may temporarily be marked by distinct enlargement and tenderness of the breast, or even by the secretion of milky fluid—"puberal mastitis." A similar transient phase of activity may occur in the new-born—"mastitis neonatorum."

Puberty past, the breast enters upon its virginal phase, which continues until interrupted by pregnancy and lactation or until the advent of the menopause. The virgin breast is generally in the state described above, and its acini are scanty and small. According to Rosenberg, however, the gland is not entirely inactive, but is subject to recurring phases of proliferation and retrogression at the menstrual periods. Coincident with ovulation and the formation of the corpus luteum the epithelium lining the terminal ducts proliferates, and the acini become increased both in size and in number. Failing impregnation, and when the stimulus associated with the menstrual period ceases, the newly formed acini shrink and disappear, and the breast returns to its normal intermenstrual condition.

In pregnancy and lactation the breast attains its zenith of physiological activity. Towards the latter part of pregnancy the cells lining the acini proliferate, and innumerable new acini bud out, pushing aside the lax peri-acinar areolar tissue and occupying every available space, even filling and enlarging the nipple. The secreting cells become columnar in shape, and almost fill the acini, and the whole picture is thus one of immense physiological activity.

Involution. At the end of lactation, and again more completely at the menopause, the breast undergoes a process of involution, whereby it becomes reduced in size, often to a thin fibrous remnant which is barely palpable even in thin subjects. The microscopic changes are varied, for involution is characterized both by atrophy and by a certain amount of proliferation. Many of the epithelial cells of the ducts and acini disappear entirely, but a few remain and may proliferate to form minute cysts or solid epithelial buds. The stroma of the breast becomes thickened by fibrosis, so that the delicate peri-acinar tissue becomes lost in bands of tough scar. The elastic lamina, previously a thin layer principally limited to the walls of the ducts, may become increased in amount and may spread around the acini. Often there is a lymphocytic infiltration of the stroma.

The involution process is one of peculiar interest in relation to many diseases of the breast. Involution changes are so common in a breast after the menopause that they are often regarded as normal, but it should be recognized that they are not merely the changes of senescence and decay. The involuting breast is the site of proliferative activity as well as of atrophy, and in some cases the proliferation may approach that seen in "chronic mastitis."

MASSIVE HYPERTROPHY OF THE BREAST

Diffuse enlargement of one or both breasts may result from tumours, cysts, or other circumscribed lesions, or it may occur as a manifestation

of general obesity, but the term "massive hypertrophy" refers to an entirely distinct condition in which there is a diffuse overgrowth of one or more elements of the mammary gland proper.

Massive hypertrophy is a very rare disease, and there are fewer than 100 authentic cases on record. Almost invariably the disease affects both breasts, though not always equally. In the great majority of cases it commences at puberty (puberal hypertrophy), but occasionally it has appeared during pregnancy or lactation.

The breasts gradually increase in size, and in the course of a year or two may attain the weight of a kilogram or even more, and hang to the level of the thighs. There is no commensurate increase in functional activity, and after childbirth there may be no secretion of milk. The skin of the breast becomes dusky and congested and sometimes thickened, and the superficial veins may be distended. The areola is enlarged and deeply pigmented. On palpation the breast is soft and sometimes nodular.

The enlargement is diffuse and affects principally the fibrous stroma of the gland, although there is also some overgrowth of the epithelial elements. Naked-eye examination reveals no characteristic change; there is nothing but "prodigious bigness." On microscopic examination there is sometimes a resemblance to the intracanalicular type of fibro-adenoma to which it may be related.

Massive hypertrophy is usually accompanied by amenorrhœa, and in some cases developmental anomalies of the reproductive organs coexist. Such features, together with the characteristic period of onset and the bilateral nature of the affection, strongly suggest that the cause is some perversion of internal secretions, probably of ovarian or hypophyseal origin.

The rapidity of the enlargement sometimes leads to a suspicion of malignancy, but actually malignant change is rare. A more important complication is infection, which may be of severe type.

ACUTE MASTITIS AND MAMMARY ABSCESS

This is an acute bacterial inflammation of the breast. Apart from rare cases in which the infection complicates tumours or cysts or other existing lesions, it occurs almost always during or shortly after the period of lactation. The causative organism is usually *staphylococcus aureus*, less commonly a *streptococcus*, and the infection is thought to reach the breast either from a fissure in the region of the nipple or along the milk ducts. In exceptional cases, unrelated to lactation, the disease may follow hæmatogenous infection, *e.g.*, in typhoid fever.

The disease takes an acute course, with swelling, engorgement, and forward projection of the breast, and with much pain and severe constitutional upset. Sometimes resolution occurs after a few days, with complete restitution of the gland to its normal state, but often suppuration ensues and a mammary abscess results.

Suppuration is favoured by the congestion of the breast and its milk content. One of the first effects of the inflammation is to obstruct

the orifices of the milk ducts, and the retained secretion, which rapidly clots, forms a fertile medium for bacterial growth. During lactation the breast is at the height of its functional activity, and its lobules contain large numbers of highly specialized, easily damaged, secreting cells. The lobules are separated and closely walled-in by tough fibrous septa. Any inflammatory swelling, therefore, is at first confined under tension, and much necrosis of the soft parenchymatous elements results. When eventually the pus bursts its confines it tracks widely through adjacent lobules, forming an irregular multilocular cavity, traversed by fibrous bands.

It is customary to describe three varieties of mammary abscess, according to their position in, behind, or in front of the gland. In an intra-mammary abscess the infection spreads from lobule to lobule, perhaps involving the greater part of the breast. Suppuration is slow to develop, and is associated with much damage to the secreting tissue. If the abscess arises superficially in the breast, or in an outlying glandular lobe in the nipple or under the skin, it rapidly spreads from the breast proper to the subcutaneous tissue—one form of *pre-mammary abscess*—and in this situation it points rapidly, with little damage and few constitutional symptoms. Pre-mammary abscesses may arise also from infection of a sebaceous gland, or from superficial cellulitis, and in such a case the breast is not affected.

A deep-seated intra-mammary abscess may spread to the loose connective tissues behind the breast—*retro-mammary abscess*. Such an abscess may have the shape of a collar stud, with a small cavity in the deeper part of the breast communicating with a larger one in the retro-mammary connective tissue plane. Rarely a retro-mammary abscess arises from other causes, *e.g.*, secondary to an infected hæmatoma or to osteomyelitis of a rib.

CHRONIC MASTITIS (Cystic Mastitis)

This is a disease of confused nomenclature, complicated morphology and baffling pathogenesis, and it has been described as the “root and centre of all difficulties in breast pathology.” It is now clearly recognized that the disease has a far greater significance than that of a mere inflammation, but its true nature is still a subject of controversy. This is reflected also in the diversity of nomenclature adopted by different writers, for cystic mastitis, diffuse fibro-adenoma, involution disease, and a host of other names have been applied. The term “chronic mastitis” is unsatisfactory, for it indicates an inflammatory lesion, but it has received general adoption, and for the present it may therefore be retained.

The features of chronic mastitis are many and varied, but three stand pre-eminent, namely (1) capricious fibrosis of the peri-acinar and periductal tissues, (2) cystic dilatation of acini and ducts, and (3) widespread proliferative changes in the epithelial lining cells.

On section, the corpus mammæ is tough and fibrous, of grey or greyish-yellow colour and of the consistency of indiarubber. It differs from a scirrhus carcinoma in lacking the stony hardness of that

condition and in containing none of the characteristic small yellow spots of epithelial *débris*. Cysts are usually, though not invariably, present. Most often they are small, only a few millimetres in diameter, and scattered through the whole substance of the breast, but occasionally there is a solitary cyst, or two or three are present, and they may attain considerable size. Rarely the whole breast is occupied by large cystic spaces (cystic disease of the breast, Schimmelbusch's disease, Réclus' disease). The main ducts of the breast are often visibly dilated, and filled with creamy fluid or soft yellow *débris*. The content of the cysts may be of similar nature, but it is usually thin and watery, either clear or slightly turbid, rarely blood-stained. When the cysts are large they project beyond the confines of the actual gland, and form tense rounded swellings. Such cysts, distended with clear fluid, have a blue colour when exposed by incision of the tissues overlying them, and have been called blue-domed cysts (Bloodgood). Sometimes the cysts contain papillomatous growths (Brodie's tumours), and although these

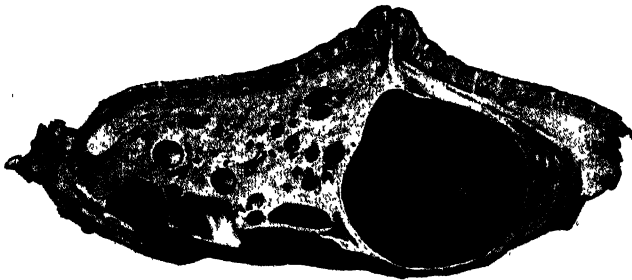


FIG. 156. Chronic mastitis. The breast is fibrous and contains numerous cysts.

(By courtesy of Mr. J. W. Struthers.)

are usually small and barely recognizable without the aid of a lens, they may occasionally attain considerable size. Thus it is possible to trace all intermediate forms between simple chronic mastitis and true benign tumours (papillomata and adenomata).

Microscopic Appearance. The microscopic appearance is very varied, both in different breasts and in different parts of the same breast. In one region fibrosis predominates, in others cyst formation, and in yet others epithelial proliferation.

(1) The fibrosis affects principally the delicate peri-acinar and periductal connective tissues. The new fibrous tissue is often infiltrated with lymphocytes and plasma cells; and the elastic lamina, previously a tenuous layer related only to the ducts, may become thickened, and may spread to enclose the acini. The cysts vary greatly in size and shape. They contain fluid and epithelial *débris*, and often large masses of cells derived from the duct wall. Some of the cysts are lined by cells similar to those of normal mammary ducts, others by somewhat larger, pale-staining, eosinophil cells. These "pale cells" closely resemble the epithelial cells of sweat glands, and have been thought to originate

from sweat-gland rests of developmental origin. It seems more probable that they are derived from the ordinary cells of the breast, itself a modified sweat gland, as a result of degenerative changes. According to Cheatle, the cysts arise principally from dilatation of the ducts, and in serial sections through the whole breast it is sometimes possible to trace the whole length of a duct with its branches and related acini as a long, tortuous, dilated channel.

The cause of the cyst formation is not definitely established. By some it is attributed to fibrosis and consequent distortion or obstruction of the ducts; by others, to excessive proliferation of the lining membrane. It seems possible that both these factors operate, for in some places the lining membrane is atrophied and flattened as though from distention, while in other parts it shows evidence of active growth and proliferation.



FIG. 157. Chronic mastitis. $\times 100$. There are several dilated ducts. Below, on the right side, the ducts are distended as though from obstruction, and their epithelial lining is flattened. Above, on the right, a dilated duct contains a laciform, papillomatous mass of proliferated epithelial cells. The connective tissue between the ducts is fibrous and is infiltrated by lymphocytes.

(Royal College of Physicians of Edinburgh.)

Epithelial Proliferation in Chronic Mastitis. The epithelial proliferation or hyperplasia is now regarded as the most important single feature of the disease. The proliferation takes many forms, all of which may be recognizable in a single breast, and there may be a continuous gradation, in different parts of the breast or in a single duct, from simple overgrowth at one end of the scale to hyperplasia indistinguishable from malignancy at the other.

E. K. Dawson recognizes two main types of proliferation, adenosis and epitheliosis. Adenosis denotes a proliferation which, though excessive in amount, still conforms to the physiological pattern, and which consists in an increase of glandular tissue somewhat similar to that found normally in pregnancy. Such adenosis may affect the whole breast or occur in localized areas. When present in excess it may lead either to a diffuse adenomatosis of the breast or to the formation of one or more localized tumours (fibro-adenoma).

Epitheliosis denotes an increase of epithelium which does not form glandular tissue of physiological pattern, but which fills up and distends existing glandular structures (ducts or acini). Such epitheliosis may consist in a simple overgrowth of the epithelial lining cells, or in papillomatous or massive proliferation.

In the papillomatous type of proliferation, the lining cells multiply

and are projected into the lumen upon delicate cores of connective tissue like multiple small papillomata. Small proliferations of this type are common in chronic mastitis, and are found either in dilated ducts or in cysts. Generally, they are found only on microscopic examination, but one or more may attain considerable size and present all the characters of a simple tumour (duct papilloma or intra-cystic papilloma).

The massive type of epithelial proliferation is the least common. The ducts are filled by solid masses of hyperchromatic cells which show every sign of rapid growth. In some cases the cells individually appear malignant, and can be distinguished from invasive carcinoma only by the fact that they are confined to the lumen and do not invade the surrounding tissues. Such a condition approximates closely to the "intraduct carcinoma" described by Muir.

Types of Chronic Mastitis. Two main forms of chronic mastitis may be recognized clinically, the localized and the diffuse. The *localized form* affects principally one segment of the breast, although microscopic examination generally shows that the changes are not entirely circumscribed, but are present over a wide area and in both breasts. The affected part forms a nodular, irregular lump in the breast, and sometimes is so hard as to simulate cancer. It may usually be distinguished, however, by the fact that although easily palpable and clearly outlined when the breast is held between fingers and thumb, it loses both its definition and its sense of induration when pressed against the chest wall. In other respects the distinction is not always easy. Chronic mastitis rarely causes retraction of the nipple or dimpling of the skin, but since these two signs may be absent in the early stage of cancer—the ideal stage for treatment—their diagnostic value is limited. Moreover, in mastitis slight enlargement of the axillary glands is not uncommon, and it may prove misleading.

The *diffuse form* affects the greater part of one or both breasts, and for this reason is less likely to be mistaken for malignant disease. The characteristic feature on examination is a diffuse, fine granularity, most easily defined when the breast is palpated between the fingers and thumb.

Cysts may occur in either type, and if large are readily palpable as smooth, tense, mobile swellings. In some cases, one or both breasts are completely cystic (Schimmelbusch or Réclus' disease).

Chronic mastitis may develop at about the period of the menopause, but often it occurs much earlier. The disease is most common in the unmarried and childless, but may arise in parous women. In the great majority of cases it is symptomless, and passes unnoticed or only attracts attention when a lump is felt in the breast. Occasionally, however, there are shooting pains, either in the breast itself or referred to the arm.

Nature of Chronic Mastitis. The nature of chronic mastitis has been greatly clarified in recent years. All the available evidence indicates that the disease is not due to bacterial infection nor to toxæmia but to the perverted action of certain hormones which normally exercise an influence upon the activities of the breast.

The breast is continuously influenced by ovarian hormones, which

are themselves subject to the control of the hormones of the anterior part of the pituitary gland. To variations in the activity of these secretions are due those proliferative changes which occur at puberty, at the menstrual periods, during pregnancy and lactation, and at the menopause. It can readily be understood, therefore, how an abnormality of this controlling mechanism may lead to the changes characteristic of chronic mastitis, changes which differ from the physiological process of involution only in their greater extent and in the predominance of epithelial proliferation rather than atrophy.

So far as our present knowledge goes both the ovarian hormones, œstrin and lutein, exercise an effect on the breast, and it is possible that pituitary hormones may act both directly on the breast and also indirectly by controlling the secretions of the ovary. In animals it has been found possible to induce chronic cystic mastitis by repeated injections of impure folliculin or œstrin (Goormaghtigh), and it seems likely that some abnormality, quantitative or qualitative, in these hormones is responsible for chronic mastitis in man.

The Relation of Chronic Mastitis to Tumours of the Breast. (1) Simple tumours. Chronic mastitis is an almost invariable accompaniment of simple tumours of the breast. Generally, it can be recognized only on microscopic examination, but in some cases its presence is quite obvious. Some authorities, indeed, recognizing the close relationship of chronic mastitis to simple tumours, regard them not as distinct conditions but as manifestations, differing only in degree, of a single disorder, a mammary dysplasia. Thus a fibro-adenoma may be regarded as an extreme, localized form of the "adenosis" found diffusely in chronic mastitis, whilst a papilloma may be regarded as an extreme, localized form of "epitheliosis."

(2) Carcinoma. The relation of chronic mastitis to carcinoma of the breast is of immense interest in its bearing upon the question of the cause of cancer, and it is also of great practical importance from the therapeutic standpoint, for upon it depends the choice, so vital to the welfare of the patient, between conservative measures and radical extirpation. In spite, however, of extensive clinical and pathological investigations the question still remains highly controversial, and eminent authorities hold opposite views, viz.: (1) that chronic mastitis is a frequent precursor of cancer, and (2) that the breast affected with chronic mastitis is little, if any, more liable to cancer than the normal breast.

The close relation of mastitis to cancer has been upheld principally by those who approach the subject from the histological standpoint, and there is no doubt that on microscopic examination the epithelial proliferation of mastitis may approximate so closely to malignancy as to deceive the most experienced pathologist. Moreover, a breast affected by carcinoma almost invariably shows evidence of chronic mastitis. These observations afford very strong support for the view that at least some forms of chronic mastitis are precancerous. Further support has recently been forthcoming from experimental work upon the hormonal origin of chronic mastitis, for it has been claimed that in mice the repeated injection of folliculin (œstrin), which has been shown

by other writers to give rise to chronic mastitis, may in some cases lead to the development of carcinoma (Lacassagne).

From the practical standpoint, however, it must be recognized that malignant change is not a regular, or even a frequent complication of chronic mastitis. The general view is that carcinoma is most likely to occur in the localized type of chronic mastitis, especially if cystic, and that it is a very rare complication of the diffusely nodular type.)

CYSTS IN THE BREAST

The great majority of cysts in the breast are those related to chronic mastitis, and have already been described in that connexion.

A rather uncommon type of solitary cyst is the *galactocoele*, or milk cyst. It develops during or shortly after lactation, probably from some obstruction to one of the principal ducts. At first the content is thin and milky, and the cyst is tense and thin walled, but finally the milk gradually becomes inspissated to a cheesy consistence, and the wall loses its epithelial lining and becomes thick and fibrous, so that it may eventually resemble, and be mistaken for, a dermoid cyst. It forms a painless, rounded swelling situated close under the nipple. At first it is tense and elastic, and is mobile within the breast. Sometimes a little milky fluid may be expressed from the nipple. Later it acquires a more solid consistence and becomes fixed to the surrounding breast by fibrous adhesions. The history of onset during lactation usually suggests its nature.

Cysts may arise in the breast in relation to tumours, and they will be described in the appropriate place. Blood cysts occasionally arise from the encapsulation of old hæmatomata. The so-called retention and lymphatic cysts are probably really cysts in connexion with chronic mastitis. Dermoid cysts have been described, as have hydatid cysts.

TUBERCULOSIS OF THE BREAST

This affection occurs principally in middle-aged women. It is generally regarded as a rare condition, though, like other forms of tuberculosis, it is not uncommon in Scotland.

The breast is usually involved by direct spread of the disease from some neighbouring structure, *e.g.*, from a rib, from a lymph gland in the axilla or from tuberculous pleurisy. Rarely, it is involved in the absence of a neighbouring focus, and the infection must be presumed to have reached the breast by the blood stream from a distant primary focus.

In the common form, secondary to tuberculosis of a costo-chondral junction, there is a deep-seated, symptomless swelling—a cold abscess—which may track forwards and downwards, involving the mammary tissue. Eventually it comes to the surface, generally at the infra-mammary fold, and gives rise to a sinus.

Less often, in the early stages a hard nodular mass may be felt in the breast, and may be mistaken for a focus of chronic mastitis or even carcinoma. It consists of an aggregation of tubercles, partly caseous

and matted together by fibrous tissue. Such a mass generally softens, and in the course of time gives rise to a cold abscess, or it may stimulate much fibrous tissue and lead to extensive sclerosis of the breast.

SIMPLE TUMOURS OF THE BREAST

These are fibro-epithelial tumours composed of various proportions of glandular and connective tissues. In the past it has been customary



FIG. 158. Pericanalicular fibro-adenoma of the breast, removed from a woman aged twenty-eight years. The tumour had grown slowly during several years. It is non-malignant, and is surrounded by a well-defined capsule of condensed fibrous tissue.

(Department of Surgery, University of Edinburgh.)

to recognize a large number of different types, but it is now admitted that many of these depend merely upon variations of degree rather than of kind, and that actually all are closely related. The most simple and generally useful classification recognizes three principal tumours, two forms of fibro-adenoma and one form of papilloma. Typically, each of these is distinguished by striking characteristics, but intermediate forms may occur in which the designation is difficult.

In regard to the ætiology of these tumours, a great advance has been achieved in recent years. By the employment of whole section, "key block," and other methods it has become possible to study the breast as a whole. Such studies show clearly that a simple tumour is rarely the only pathological lesion, but is often accompanied by changes of the nature of chronic mastitis in the rest of the breast; and there is much evidence to suggest that the two lesions are connected, and that the tumour may be regarded as a very localized and extreme form of the same proliferative changes as are found in chronic mastitis.

Simple tumours other than fibro-adenoma and papilloma are rare. Fibroma, adenoma, lipoma, myxoma, and angioma have been described.

Fibro-adenoma

Two principal types of fibro-adenoma are recognized: (a) pericanalicular and (b) intracanalicular.

(a) **Pericanalicular Fibro-adenoma.** A pericanalicular fibro-adenoma occurs typically in young women from twenty to thirty years of age,

though occasionally later in life. It is usually small, firm, and of slow growth (hard fibroma), but may be softer, even to the softness of a lipoma. It is rounded or ovoid, and almost invariably encaps-



FIG. 159. Pericanalicular fibro-adenoma of the breast. Acini lined by a single layer of columnar or cubical cells lie embedded in a fibrous stroma.

(Laboratory of Royal College of Physicians of Edinburgh.)

suled, and is usually recognizable on clinical examination by its great mobility within the substance of the breast. When the capsule is opened and incised the tumour may be enucleated like a pea from its pod, and like the pea it has a pedicle of attachment where its vessels enter.

The pericanalicular fibro-adenoma is believed to arise as a result of an extreme but localized proliferation comparable to the "adenosis" of chronic mastitis (p. 367). It is as though a ductule

or a number of related ductules bud out into innumerable new acini, which fill the "accommodation space" and hollow out a cavity for themselves within a capsule formed by the surrounding fibrous tissues.

The microscopic structure is extremely simple, for the tumour consists of a variable amount of fibrous tissue in which are rounded or oval acini lined by cubical epithelium. Depending upon the amount and nature of the connective tissue, the tumour is soft or hard. Occasionally, when the stroma is scanty, the appearance is that of an adenoma, and when the stroma preponderates the tumour may have the character of a fibroma.

(b) **Intracanalicular Fibro-adenoma.** An intracanalicular fibro-adenoma differs, in typical examples, both in appearance and progress. It occurs commonly at a later age period, between thirty and fifty years of age, and grows somewhat rapidly. The consistence is soft, and eventually the tumour may attain great size, and is liable to be mistaken for sarcoma. On cross section the tumour often appears partly cystic and partly solid, and in places the solid portions project into the cysts in the form of bulky cauliflower-like processes of complicated structure (*cystadenoma* or *intracystic papillary adenoma*).

The tumour probably arises from overgrowth of the delicate connective tissue immediately outside the ductal epithelium. In its growth this tissue projects into ducts and dilated spaces in a complicated mass of blunt, rounded processes, each covered with epithelium. With



FIG. 160. Intracanalicular fibro-adenoma of the breast. The tumour forms a cauliflower-like growth and fills and distends the cyst in which it lies.

(Department of Surgery, University of Edinburgh.)

increase in size these processes adhere and form secondary attachments to the duct or cyst walls. This complex three-dimensional growth is not easily recognizable in sections, and microscopically the tumour consists merely of large tracts of connective tissue containing slit-like, semilunar or irregularly branching spaces lined by cubical epithelium. The connective tissue of the tumour is extremely delicate, of almost myxomatous appearance, and it may be so cellular as to resemble sarcoma. Sarcomatous change occasionally takes place (*adenosarcoma*).

The tumour at first is mobile and on incision it may be shelled out from a definite capsule. With increase in size it becomes irregularly lobulated, and its shape is modified by cyst formation. Later it may adhere to the deep surface of the skin, and by pressure may ulcerate through the skin, and project as a soft, fungating mass. This appearance, now rarely encountered, may suggest malignancy, hence the old name "cysto-sarcoma fungoides."



FIG. 161. Intracanalicular fibro-adenoma of the breast. $\times 100$. There is an overgrowth of lax, oedematous, connective tissue, and this, projecting into the dilated mammary ducts in complex fashion, has carried with it a covering of cuboidal epithelium.

(Laboratory of Royal College of Physicians of Edinburgh.)

Duct Papilloma (Intracystic Papilloma)

This is an epithelial tumour arising from the lining cells of a large duct, and projecting into the lumen of the duct, which coincidentally becomes dilated or even cystic. It is slow-growing, and occurs usually about the period of the menopause, though occasionally in younger women.

It is recognizable as a rounded mass of any size up to that of a hen's egg, generally situated close under the nipple, which may be unduly prominent or retracted. Associated with the tumour there is a discharge of clear or sometimes blood-stained fluid from the nipple.

On cut section the tumour is seen as a papillary growth projecting from the wall of a dilated duct. It may be small in comparison with



FIG. 162. Duct papilloma of the breast—5/6 natural size. The tumour has projected into and distended one of the main ducts of the breast. The duct is cut across in two places, in the nipple and deeper in the breast, and portions of the extensive papilloma are seen in each situation. The underlying breast shows very well the "adenosis" of chronic mastitis.

(Laboratory of Royal College of Physicians of Edinburgh.)

the dilated space or it may occupy the entire cavity, to which it is often adherent at numerous points.

Microscopically, it consists of a complex dendritic core of delicate connective tissue surmounted by hyperplastic columnar epithelium either in a single layer or, more frequently, several cells in depth. Usually only one palpable tumour is present in the breast. Rarely there may be two or three of approximately equal size. As Cheate has emphasized, however, careful examination frequently reveals early changes of a similar nature widely distributed throughout the breast.

A duct papilloma is very apt to undergo malignant change into a slow-growing cancer; a change sometimes indicated by the occurrence of a bloody discharge from the nipple. Some authorities believe that duct papilloma is itself in the early stages of malignancy. It is certainly to be regarded as precancerous.

MALIGNANT TUMOURS

CARCINOMA

Four of every five tumours in the breast are malignant, and of these the vast majority are carcinomata. Sarcoma and other rare growths account for only 3%. Carcinoma of the breast is, moreover, one of the commonest of all malignant tumours, sharing this distinction with carcinoma of the uterus, but fortunately, owing to its accessible position and comparatively slow growth, its recognition is often possible in the early stages, at a time when it is amenable to treatment.

The disease is almost limited to women, and less than 1% of cases occurs in men. It appears most commonly between the ages of forty



FIG. 163. Intraduct cancer of the breast. $\times 60$. Two of the ducts are occupied by solid masses of epithelial cells, which have all the characters of malignant cells except that they do not invade the surrounding tissues. The other two ducts are dilated and contain cells of colostrum type. Their lining cells show early proliferative changes.

(Laboratory of Royal College of Physicians of Edinburgh.)

and sixty, but it has been known to arise at the early age of seventeen, and it is not uncommon in the aged. Nulliparæ are somewhat more liable to be affected than multiparæ, owing perhaps to the frequency of chronic mastitis in the former.

Types of Mammary Carcinoma. In the past an extremely complicated classification of carcinoma of the breast has been adopted, but nowadays the whole trend of informed opinion is in favour of simplification.

The extensive researches of Cheate and Cutler, Dawson and others have demonstrated that the tumours so variously described are not distinct neoplasms but variations from a common type, and that the differences in histological structure are variations in degree rather than in kind.

The subject can best be studied by considering the early phases in the development of a tumour from its original cell or cells. It may be

assumed that practically all carcinomata in the breast arise from the epithelium of the duct system or of cysts derived from the duct system. They may all, therefore, be regarded as forms of *duct carcinoma*, although this term is used by some authorities in a more limited sense, to signify tumours characterized microscopically by duct- or tubule-formations.

The original epithelial cells, when stimulated to malignancy, may at first proliferate entirely into the lumen of the duct or cyst, without invading the surrounding tissues. To this condition of intraductal malignant epithelial proliferation Muir has applied the term *intraduct carcinoma* (see Fig. 163). Such proliferation may occur diffusely, affecting a large number of cells simultaneously in more than one part of the breast. In some cases it gives rise to a localized tumour, an *adenocarcinoma* characterized microscopically by the presence of tubules lined by several layers of hyperplastic epithelial cells (see p. 380).

The next stage in the progress of the malignant cells is seen when they penetrate the basement membrane of the duct wall and invade the surrounding connective tissues. With the assumption of invasive character, both the microscopic picture and the degree of malignancy show an immediate change. The cells, originally cylindrical, now by mutual pressure assume a spheroidal shape, and they no longer give rise to tubular or acinar formation but grow into the tissue and lymph spaces in the form of solid processes. In this way originate the various forms of *spheroidal-cell carcinoma* of the breast, a term which embraces the common scirrhus tumour and rare forms such as the encephaloid carcinoma and the acute carcinoma of lactation.

The malignancy of the various forms of invasive carcinoma of the breast depends to a remarkable extent upon the functional activity of the affected gland. In an atrophic breast, of diminished vascularity and scanty lymph drainage, the malignant cells progress slowly and become enveloped in a stroma of dense fibrous tissue (*atrophic scirrhus carcinoma*); whereas in a well-developed breast, of full vascularity and free lymph drainage, the progress is rapid, the malignant cells grow in large solid masses, and the stroma is scanty (*encephaloid or medullary carcinoma*). The most malignant mammary carcinoma is that which affects the gland in pregnancy or lactation, when its functional activities are at their zenith, and its high vascularity and copious lymph drainage promote intense proliferation and early dissemination.

Scirrhus Carcinoma

A hard or scirrhus carcinoma is the commonest form of mammary growth, occurring characteristically in women between the ages of thirty-five and sixty-five. The growth is situated most often in the upper outer quadrant of the breast; least often the lower inner quadrant is affected, while the other two quadrants take an intermediate position as regards incidence. Usually the growth arises in the substance of the gland fairly close to the nipple, but occasionally an outlying lobule is affected first. In the axillary prolongation of the breast a tumour

may be mistaken for an enlarged lymph gland. Rarely both breasts are affected simultaneously or in succession—a remarkable exception to the general rule, which suggests that cancer may depend upon some general upset of cellular activity as well as upon a local growth perversion.

Characteristically, the tumour is of small size, and is stony hard, so that it is most evident when the breast is pressed by the flat of the hand against the chest wall. From the first it is firmly fixed within the breast substance, and later, from contraction of its tough fibrous stroma, it pulls upon surrounding structures. When the tumour is related to the larger milk ducts it may cause some elevation and fixity of the nipple at quite an early period. Later the nipple becomes deeply retracted. By traction exerted upon the ligaments of Cooper the skin over the tumour may become dimpled, and later adherent. Eventually

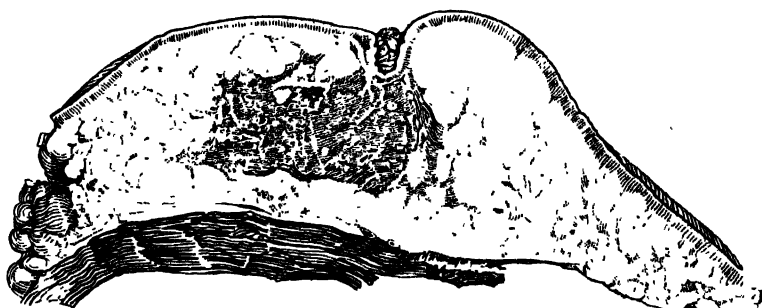


FIG. 164. Scirrhus carcinoma of the breast. The tumour possesses no capsule and has infiltrated the tissues of the breast. The nipple is deeply retracted.

(Department of Surgery, University of Edinburgh.)

the tumour becomes fixed and immobile upon the chest wall, and it may ulcerate through the skin surface.

When the breast is cut across, the nature of the tumour is usually obvious. It is so hard that the knife may creak in the process of cutting, and impart an almost gritty sensation. In the bisected breast the tumour is seen to be of small size, but invading the breast in all directions, and it has no capsule. It is fibrous, light grey or pinkish grey in colour, and it retracts somewhat when cut, so that the cut surface becomes slightly concave. Scattered through the tumour there are often pale fibrous streaks and pin-head yellow spots of necrotic epithelial tissue, so that the appearance is aptly comparable to the cut surface of an unripe pear.

Microscopically, the tumour is composed of spheroidal epithelial cells in a stroma of fibrous tissue. The spheroidal cells are believed to be derived from ductal epithelium, but they exhibit no glandular arrangement and lie simply in solid masses or in finger-like columns which invade the surrounding tissues in all directions. The stroma is present in abundance and is composed of tough fibrous tissue, hence the hard or scirrhus nature of the tumour. The elastic lamina of the ducts shows striking (and unexplained) overgrowth. Often towards the periphery of the tumour, however, the stroma is less dense and the

epithelial cells are present in greater numbers, as though more vigorous and invasive in this region. In such places the microscopic appearance may resemble that of an "encephaloid" tumour.

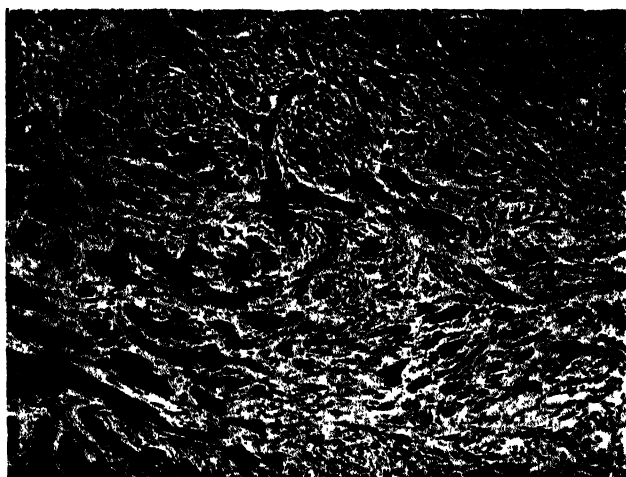


FIG. 165. Scirrhus carcinoma of the breast. Invading columns of malignant cells surrounded by a dense stroma of fibrous tissue.

The atrophic scirrhus cancer is an extreme variety of the ordinary form. It is found in atrophic breasts, and especially in women over the



FIG. 166. Encephaloid cancer of the breast. The tumour is of large size and has undergone extensive necrosis, with the formation of a spurious cyst. It has invaded the pectoral muscle and has begun to ulcerate at the skin surface.

(Department of Surgery, University of Edinburgh.)

age of sixty-five, and it forms a tumour of very slow growth and low malignancy.

The breast is shrunken, the nipple deeply retracted, and the skin over the tumour deeply puckered. The tumour is small, but very hard

and fibrous, and is firmly adherent. Metastases develop only after a long period, and death may be delayed for as long as fifteen years. Microscopically, there are small islands and delicate strands of spheroidal epithelial cells embedded in dense fibrous tissue.

Medullary (Encephaloid) Carcinoma

The medullary or encephaloid carcinoma has the same essential nature as the scirrhous variety, but it is softer, more cellular, and more rapid in growth and dissemination. It occurs typically in well-developed breasts in younger women, and forms a large soft mass that infiltrates

widely. When cut across, it is of spongy texture, or almost brain-like, and hæmorrhages and large areas of necrosis are common. Microscopically, it is composed of solid masses of epithelial cells supported in a delicate connective-tissue stroma. The epithelial cells are spheroidal or sometimes almost columnar, and may show mitotic figures and other evidence of rapid division. The tumour is often vascular, and the blood vessels are thin walled, and bleed readily.

The acute cancer of pregnancy and lactation represents an extreme form of the encephaloid type. It is a highly malignant tumour, which grows rapidly to large size, and leads to an early fatal issue, often in the course of a few months. The breast becomes diffusely swollen and painful, and dilated veins appear under the skin. The tumour is very vascular, and since there is already a state of physiological hyperæmia the whole breast becomes hot. A slight rise in body temperature may be observed, with impairment of appetite and malaise, and consequently the tumour may be mistaken for a deep-seated abscess and incised.

On cross section the tumour presents a soft, hæmorrhagic, infiltrating mass, often with large areas of necrosis. Microscopically, the epithelial cells show every sign of extreme malignancy. Mitotic figures of irregular pattern are common, nuclei stain deeply, and the cells vary greatly in size and shape. The anaplasia may be so great that the tumour resembles a sarcoma.

It should be mentioned that a mammary carcinoma arising in

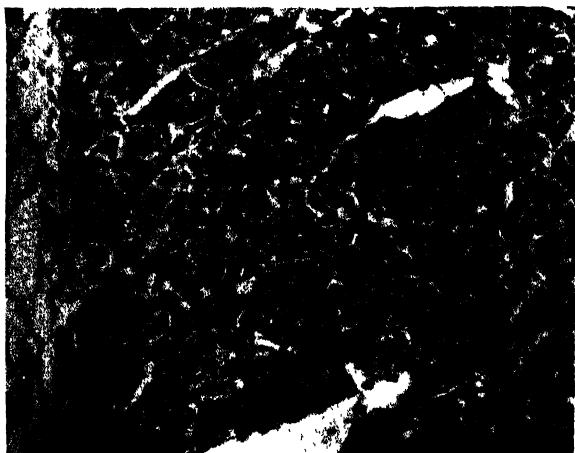


FIG. 167. Acute lactation cancer of the breast. $\times 300$. The tumour is one of great malignancy. The cells are of primitive character, and there are numerous mitotic figures. A malignant giant cell is present.

(Laboratory of Royal College of Physicians of Edinburgh.)

pregnancy or lactation does not invariably progress so rapidly. A moderately prolonged survival after operation is not rare.

Adenocarcinoma

This term was used by Halsted to describe mammary tumours containing large tubular spaces lined with many layers of epithelial

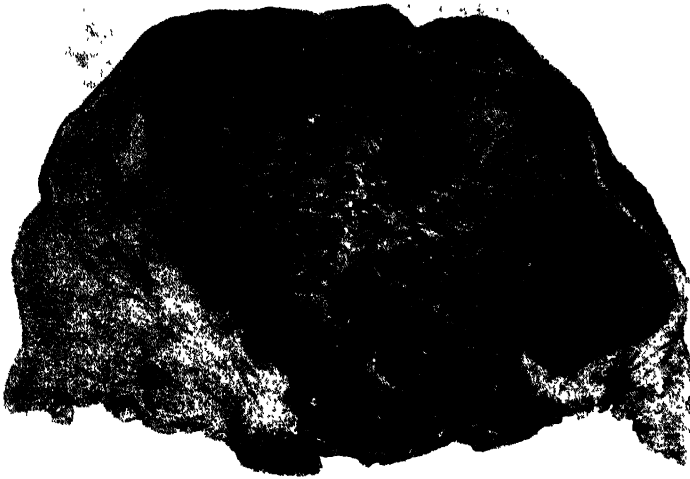


FIG. 168. Mucoid (colloid) cancer of the breast. The tumour is an adenocarcinoma that has undergone mucoid change, and it contains numerous cystic spaces filled with jelly-like material. Though massive, it is fairly well circumscribed and not very malignant.

(Department of Surgery, University of Edinburgh.)

cells. It is now generally applied to a tumour in which the cells are not entirely arranged in solid masses, but exhibit in places a glandular arrangement. In most cases a tumour of this class approximates to a localized form of intraductal malignant hyperplasia (*see* p. 376) and is consequently of low-grade malignancy. Some such tumours are partly composed of large, clear rounded cells, resembling sweat gland cells. Tumours of this type have been described as "sweat-gland carcinoma" and have been regarded as arising from sweat-gland rests isolated during development (Creighton). In Dawson's opinion, on the contrary, the tumours are derived from the ordinary epithelial cells of the breast, and the pale appearance of the cells results from degenerative changes. It is possible that other adenocarcinomata arise from the malignant transformation of papillomata in ducts and cysts.

Mucoid Carcinoma (Colloid or Gelatinous Carcinoma). Small areas of mucoid degeneration are not uncommon in mammary growths, and occasionally this change is sufficiently obvious to merit separate description. In well-marked examples a large area or even the entire tumour is affected. The mucoid material is a product of the malignant

epithelial cells. At first it lies within the cells, which as a consequence become distended to signet ring shape. Later the mucoid material is set free in the intercellular stroma, sometimes in such large quantities as to obscure the small and more or less degenerated epithelial cells.

Mucoid cancers are usually bulky and of soft consistency, but their apparent malignancy is usually belied by slow growth and late dissemination. Occasionally, however, they are rapidly invasive.

When cut, the tumour is seen to be composed mainly of soft, jelly-like material, yellow or red in colour, often collected in cyst-like spaces. In places there are masses or streaks of solid tumour tissue of pale colour. Microscopically, there is sometimes difficulty in recognizing the nature of the tumour, for many of the epithelial cells are degenerate, and are scattered as small islands in homogeneous jelly-like areas of mucinous substance.

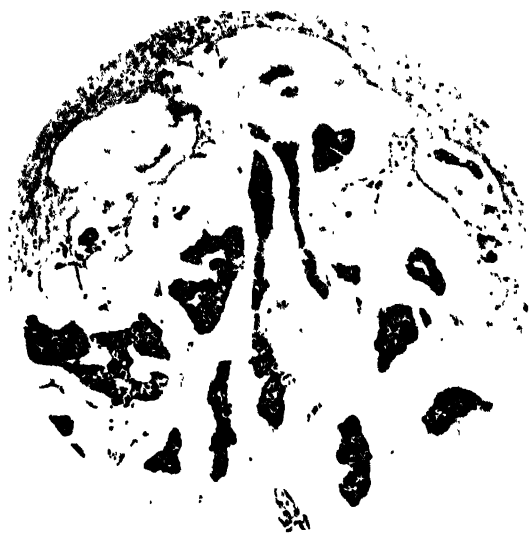


FIG. 169. Mucoid cancer of the breast. $\times 80$
Small collections of spheroidal epithelial cells are surrounded by masses of mucoid (colloid) material.
(Laboratory of Royal College of Physicians of Edinburgh.)

CARCINOMA OF THE MALE BREAST

Cancer of the male breast is rare, no doubt for the reason that it is exempt from the physiological stresses to which the female breast is subject. It is significant that gynecomastia is present in a considerable proportion of cases. In general character the tumours correspond to those of the female breast, and they are usually of slow-growing scirrhus type. Most cases occur between the ages of fifty and sixty years. Not infrequently the breast has been subjected to constant or repeated trauma, often occupational—for example, by the pressure of a bootmaker's last. Rarely the carcinoma takes origin in a simple tumour of long duration. Since the male breast is of small dimension the tumour early transgresses its limits and invades the pectoral muscles, the skin and the lymph glands. (This early spread, together with the technical difficulty at operation of excising a sufficiently wide margin of healthy tissue from the thinly clad male thorax, renders the prognosis somewhat more grave than in the female.

SPREAD OF CARCINOMA OF THE BREAST

The methods and routes of spread of carcinoma of the breast have been the subject of prolific research and much well-established information has resulted. The pathological and surgical importance of the subject requires no emphasis.

Spread *viâ* Lymph Vessels. This is by far the most important route for dissemination in cancer of the breast, just as it is in any other carcinoma.

The actual mode of lymph vascular dissemination remains a controversial subject. According to Handley's theory of lymphatic permeation, the growing neoplasm permeates surrounding tissues in delicate invading columns, which extend by a continuous multiplication of its advancing cells. This invasion takes place radially in all directions, whether in the direction of the normal flow of lymph or against it. As the rapidly growing cells at the head of each column progress, the cells further back undergo degeneration as a result of reactive fibrosis, so that, while the peripheral growth extends, the more centrally placed portions are obliterated. Thus there is formed a more or less circular zone of actively progressing malignant disease, a "neoplastic ringworm," which gradually increases in diameter and tends to form secondary nodules in skin, bones and viscera at progressively greater distances from the primary growth.

Handley has offered a mass of interesting evidence in support of this theory. He has emphasized that the earliest metastatic nodules in the skin are found close to the breast or in the scar of operation, whereas later the skin further distant may be involved. Similarly, metastases in bone, he claims, occur first in the ribs, sternum and vertebræ, later in the upper ends of the humerus or the femur, and rarely at more distant situations. Furthermore, metastases in bone occur most often on the same side as the primary growth. The upper end of the femur, for instance, is involved three times more commonly on the same side as the primary tumour than on the opposite side.

In recent years, however, the permeation theory has suffered contradictions. Microscopically, it is usually impossible to demonstrate evidence of destruction of malignant cells and obliteration of lymph vessels within the spreading circle, and on the contrary the tissues close to a primary growth are usually more heavily infiltrated with malignant cells than those more distant. Comparison with the mode of spread of carcinoma elsewhere, *e.g.*, in the tongue, does not support Handley's hypothesis.

It is now generally believed that extension *viâ* the lymph vessels depends principally upon a process of embolism, cancer cells or masses of cells being detached from the parent growth and set free in the lymph stream. They are carried first along the periductal lymph vessels to the subareolar lymph plexus (Sappey), or to the extensive plexus of lymph vessels in relation to the deep fascia. Thence they are carried to the regional lymph glands. In the early stages the most important dissemination is to the axillary glands. "Leaf's gland," close to the axillary tail of the breast, and the pectoral group

of axillary glands are usually affected first. From these there is extension to other groups of axillary glands and later through the apex of the axilla to the supraclavicular glands. Occasionally the primary tumour spreads directly to glands of the apical group by lymph vessels that penetrate the greater pectoral muscle and the costo-coracoid membrane. The small collection of glands in the infraclavicular triangle may be infected by the same route.

A growth in the medial half of the breast often disseminates early to the glands situated along the internal mammary artery, and these in turn readily infect the mediastinal glands, the pleura and lung.

Tumours in the lower medial quadrant of the breast are situated, as Stiles pointed out, immediately superficial to the sheath of the rectus muscle, and not far distant from the epigastrium, so that dissemination *via* this "dangerous angle" is relatively frequent. The peritoneum may be invaded by malignant cells, which form either multiple small scattered deposits or a few large masses in the omentum or on the pelvic floor. The liver, often the first viscus to be affected, may be invaded from its peritoneal surface, and is usually riddled with deposits.

In advanced cases, and rather uncommonly, the disease may spread by lymph channels across the mid-line, to affect the opposite breast or its axillary glands.

Involvement of Skin. The skin may be affected in several ways, either by malignant invasion or as a secondary result of obstruction of lymph vessels in the corium.

(1) Direct invasion is particularly apt to occur if the primary tumour is situated superficially. The overlying skin is thinned and later ulcerates. In the scirrhus varieties of tumour the ulcer may resemble a squamous cell carcinoma, with indurated, rolled edge and a raised sloughing base. More bulky tumours tend rather to project as soft, fungating, often hæmorrhagic masses.

(2) Multiple metastatic nodules may appear around the tumour, either in a healthy area of skin or in parts modified by lymph vascular obstruction. At first, they tend to appear close to the primary tumour or, after operation, in or close to the scar; later, they may extend to cover large areas of the thorax and abdomen. According to Handley, the nodules result from the invasion of the skin from below, by cells derived from the growing edge of the annular zone of permeation along the deep fascia.

(3) *Peau d'orange*. In this affection the skin becomes tense, thickened and œdematous, not from true cancerous invasion but from obstruction of deep lymph channels by the malignant growth. The tiny pitted depressions that mark the site of hair follicles and sweat glands give the appearance of pigskin or orange peel.

(4) *Cancer en Cuirasse: Cancerous Pachydermia*. This is a curious condition of the skin occurring, somewhat rarely, in the late stages of the disease, and especially in relation to a carcinoma of a slow-growing scirrhus type. The first change is a retraction of the skin immediately superficial to the growth, which becomes fixed and indurated. The change progresses until it may affect the greater part of the thoracic and abdominal surface. The arm of the same side is almost invariably

affected, the opposite one not infrequently. The affected skin is at first thick and œdematous, pitting on pressure. Later, it becomes shrunken, tense, and as hard as leather, so that eventually the trunk is enclosed in a semi-rigid case, which may be so tightly stretched as to interfere with respiration. Scattered over the affected skin there are often secondary cancerous nodules, which may be pale, pigmented or hæmorrhagic. "Cancer en cuirasse" is believed by some to arise from a widespread infiltration of the skin by a very scirrhus growth. Others regard it as secondary to the œdema of lymphatic obstruction.

Dissemination to Bones. It has already been remarked that metastatic deposits in bone occur most frequently in the vertebral column, less often in the upper ends of the humerus and the femur and the skull, and only rarely in more distant situations. Handley claimed that this distribution is clear confirmation of the method of spread by lymph vascular permeation. Pincey, however, believes that it can be explained on the basis that all these regions in the bones normally contain red bone marrow, and that blood-borne cancer cells grow most readily in this tissue. The first sign of a metastasis in bone is found in the centre of the marrow, with no trace of invading columns of cells between it and the periosteum. Similarly a metastasis in the cranial bones always commences in the diploë.

Dissemination by the Blood Stream. In addition to the secondary deposits in bone, it is generally believed that a certain number of other metastatic growths, especially in the lungs and brain, arise from emboli disseminated by the blood stream. Schmidt showed, many years ago, that such emboli can be demonstrated frequently in the pulmonary vessels at the time of death, and although, as he believed, many of these are walled off by a protective sheath of blood clot, it seems likely that some few may engraft on the wall of the vessel and produce a secondary growth.

SARCOMA

The activities of the breast are related principally to its epithelial elements, and it is therefore not surprising that connective tissue tumours are much rarer than carcinoma.

Sarcoma accounts for about 3% of all mammary tumours. It may arise *de novo* in the breast, and is then either of spindle-cell or round-cell type, or it may represent a malignant change in a pre-existing fibro-adenoma of the intracanalicular type (adeno-sarcoma). In this latter variety both ectodermal and mesodermal elements are present, and the spindle cells, large or small, may be arranged around ducts or spread diffusely. The two types are distinguishable clinically only by the longer history of the latter variety. Both form rapidly growing massive fleshy tumours, which infiltrate the breast, and lead to metastases in the lungs or other viscera.

RARE TUMOURS IN THE BREAST

Teratoma of the breast is of rare occurrence in man, though common in dogs. Islands of cartilage, calcified areas, and sometimes

bone, are found scattered through a stroma of actively growing spindle cells. The tumour is usually malignant, and resembles sarcoma in its course. Its chief interest lies in its origin. It probably arises in the same way as similar tumours in the mediastinum, from displaced totipotent cells.

Squamous-cell carcinoma may arise from the skin, the areola, the nipple or the terminal portions of the milk ducts. *Melanoma* and *malignant angioma* have been described.

TRAUMATIC FAT NECROSIS

This is an affection of adipose tissue which is especially apt to occur in the neighbourhood of the breasts, particularly in obese women. It is in no sense an affection of the mammary gland, but as it is apt to be mistaken for carcinoma, it may conveniently be considered here.

The disease was first recognized in 1896 by Shattock, who described an example occurring in relation to a lipoma in the buttock, and the name, "traumatic fat necrosis," was assigned to it by Lanz in 1898. In recent years Lee and Adair have described a number of cases and have drawn attention to its frequency and to its tendency to simulate cancer.

In about 50% of cases the lesion follows some known injury, either a direct blow or, not infrequently, the trauma associated with subcutaneous administration of saline solution. It is possible that in the remainder the causative factor is some minor but oft-repeated trauma such as may result from the pressure of clothing or the drag of a heavy, pendulous breast. A few weeks after the injury, or occasionally much later, a lump develops in the breast or in the subcutaneous tissue close to it. The lump is moderately well circumscribed and is of stony hardness, and adherent to the breast and surrounding tissues. In about half the cases the skin overlying it is tacked down and sometimes there is a pigskin appearance like that in cancer. Occasionally the nipple is retracted.

When cut across, the lump is seen to be composed of tough fibrous tissue, in the centre of which are pale chalk-like areas and spaces containing liquefied fat. It may be distinguished from cancer by the absence of the characteristic small yellow spots of epithelial *débris*, and by the fact that though adherent to surrounding tissues it does not infiltrate them.

The essential pathological feature is a slow aseptic saponification of neutral fat. In the centre, fat is liquefied, and around it the products of saponification excite a foreign body reaction. Microscopically, globules of fat, fatty acid crystals and sometimes calcium deposits are evident at the centre, and around them is a large mass of young fibroblastic tissue. Many phagocytic cells are seen filled with fat globules and usually there are numerous giant cells of the foreign body type.

PAGET'S DISEASE OF THE NIPPLE

This is a rare disease of middle-aged and elderly women, characterized by an eczematous affection of the nipple, which coexists with or is followed by a carcinoma in the breast. The condition begins at the



FIG. 170. Paget's disease of the nipple. $\times 80$. The inter-papillary processes of the epidermis are enlarged, and contain the typical Paget's cells. There is a lymphocytic infiltration of the corium.

(Laboratory of Royal College of Physicians of Edinburgh.)

nipple, which assumes a bright red, florid, finely granular surface, well defined at its margins, and covered by dry scales or exuding a clear or sanguineous discharge. The lesion is slowly progressive, over a period of months or years, eventually eroding the nipple and covering the areola and the surrounding skin over an area which may attain a diameter of 4 or 5 cm.

Microscopically, there are several characteristic changes both in the epidermis and in the true skin.

(1) The epidermis, ulcerated superficially, at the same time undergoes proliferative changes, which become evident on its deep aspect, where the inter-papillary processes become increased in depth and in breadth (see Fig. 170).

(2) The most characteristic feature is the occurrence of "Paget's cells," which lie singly or in small groups in the deeper parts of the epidermis, especially in the prickle-cell layer. The cells are at first large and rounded, with the appearance of cells of an undifferentiated glandular carcinoma, but they rapidly undergo retrogressive changes and assume a hydropic, degenerated appearance (see Fig. 171).

(3) Coincidentally there are changes in the true skin. Collections of lymphocytes and plasma cells appear in the papillæ of the corium, the capillaries may be dilated, and there is often a fibroblastic reaction. These changes are believed by some to precede the epidermal lesions and to be important features of the whole process. Others regard them as the results of an almost inevitable mild infection of the free surface.

(4) Along with these lesions at the nipple there are almost always proliferative changes in the underlying breast. The ducts are dilated or cystic, and various degrees of epithelial hyperplasia may be present.

Ætiology. The nature of the disease has been the subject of much controversy, and still remains unsolved. Particular interest attaches to its relationship to the underlying carcinoma. A subadjacent carcinoma almost invariably occurs, sometimes shortly after the appearance of the affection of the nipple, usually within two years, but occasionally as long as ten or even twenty years later. The tumour, which is usually of the slow-growing, scirrhus variety, may arise in any part of the breast, and may be at some distance from the nipple.

According to Handley, the nipple lesion is due to œdema of the epidermis resulting from obstruction of the lymphatics by the deep-seated carcinoma.

The theory more widely accepted is that propounded by Muir. Muir emphasizes that in every breast affected by Paget's disease examined by him there has been present a widespread hyperplasia of the epithelium lining the ducts—the condition he describes as “intraduct cancer” (p. 376). This hyperplasia is the primary factor which leads to the development both of the nipple lesion and also of the underlying scirrhus carcinoma.

According to this theory, hyperplastic epithelial cells derived from the milk ducts close to the nipple invade the epidermis and lead to the ulcerative lesion in that area. These invading cells form the “Paget cells,” and their peculiar hydropic appearance is due to degenerative change induced by the reaction of the epidermis.

Similarly, hyperplastic epithelial cells in one of the ducts deep in the breast may also assume invasive characters, penetrate the duct wall and give rise to the formation of a scirrhus carcinoma.

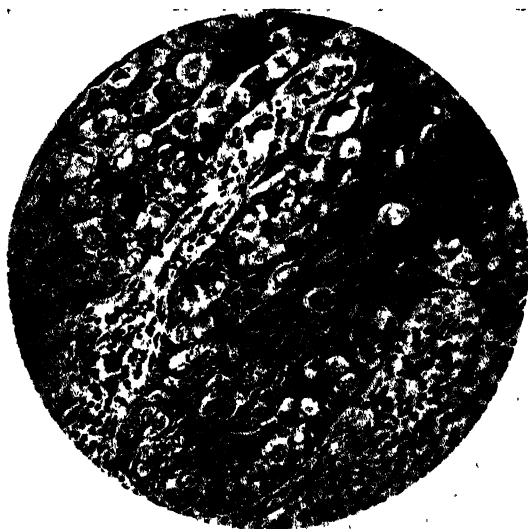


FIG. 171. Paget's disease of the nipple. $\times 175$. The section shows two interpapillary processes of the epidermis containing numerous Paget cells. Note the lymphocytic infiltration in the corium.

(Laboratory of Royal College of Physicians of Edinburgh.)

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CHAPTER XVIII

DISEASES OF THE MOUTH, JAWS, SALIVARY GLANDS AND NECK

DISEASES OF THE LIPS

Carcinoma

CARCINOMA of the lip is a common condition which arises most often between the ages of fifty and seventy years. In over 90% of cases the male sex is affected, and in a similar proportion the growth is situated on the lower lip, especially at a point between the midline and the angle of the mouth.

Carcinoma of the lip is rare in members of the upper classes and in townspeople. It occurs most frequently in countrymen of the working classes, especially in those exposed continuously to sunlight. It is generally believed that the common predisposing factor is chronic irritation and hyperplasia consequent on the use of a hot tobacco pipe, especially of the short clay variety. This habit explains the common situation and incidence of the growth. In this connexion it is interesting to observe that in women the disease is almost limited to pipe smokers. Whilst the ætiological significance of pipe smoking is generally assumed, it is not accepted by all authorities, and Broders, in particular, has maintained that the relationship is more apparent than real. Lane Claypon, moreover, has shown that statistically there is no support for the belief that smoking, as such, has any definite relationship to cancer of the lip, though it is possible that the heat of a pipe stem or the excoriation induced by adhesion of cigarette paper may be predisposing factors. In some cases a syphilitic lesion, a wart or fissure or patch of leucoplakia, seems to be a predisposing factor.

Occasionally a growth on the lower lip is accompanied by one in a corresponding position on the upper lip, an occurrence usually attributed to implantation of free malignant cells on the opposed surface.

Naked-eye Appearance. In appearance the carcinoma may at its onset take one of several forms. Generally the tumour appears as a small warty growth projecting from the surface of the lip, accompanied by a button-like induration of the subjacent tissue. Less often it appears as a fissure which fails to heal and becomes indurated. Yet again it may be ulcerated from the start and form a small erosion which crusts over but persists and enlarges.

Later in its course the growth may assume either of two forms, the papillary and the ulcerative. (1) *The papillary form* has the appearance of a wart-like thickening, elevated above the surface. It extends slowly with little surrounding infiltration, and it is slow to invade the deeper structures. Eventually it ulcerates and then

follows the usual course of the second form. (2) *The ulcerating form* is more common. It has the appearance of a typical malignant ulcer, with a raised, irregular, rolled margin and a red, indurated base.

Microscopic Appearance. The growth has the structure typical of a squamous-cell carcinoma or acanthoma (prickle-cell tumour). The malignant epithelial cells burrow deeply in the form of pointed or finger-shaped processes which penetrate in all directions. Many of the cells have the characters of prickle cells, and cell nests are common. Often a striking feature is the aggregation of numerous small

round cells of lymphocyte type in the connective tissues close to the tumour.



FIG. 172. Squamous-cell carcinoma (epithelioma) of the lip in a farm-labourer aged forty-nine years. Note the typical situation of the tumour, to one side of the lower lip. The lip was extensively indurated and the ulceration had spread on the lingual aspect almost to the alveolar margin.

The characters of the tumour cells vary somewhat in different tumours according to the degree of malignancy. In rapidly growing tumours the cells assume anaplastic characters and revert to a primitive type, whereas in less active tumours they present various degrees of differentiation and tend to become keratinized and to form cell nests. Broders has made use of these variations and has formulated a method of

grading the tumours according to the degree of differentiation present (*see* p. 57). Tumours of grade 4, in which 75% or more of the cells are undifferentiated, have very malignant characters, whereas tumours of grade 1, in which fewer than 25% of the cells are undifferentiated, are less malignant (*see* Figs. 17 and 18). Tumours of grades 2 and 3 occupy intermediate positions.

Mode of Spread. The growth spreads in the substance of the lip and destroys it, and eventually it may invade the cheek, gum and alveolus. Superadded infection is common, and the ulcer discharges thin pus mixed with copious saliva. Often the breath is foul. The growth disseminates, often at an early stage, to the regional lymph glands. The glands of the submandibular and submental regions are usually affected first, and later those of the upper deep cervical group or, less often, of the lower part of the neck. Distant metastases are uncommon, and death is usually the result of superadded septic infection or of septic pneumonia.

Primary Syphilis of the Lip

The lip is the commonest site of extra-genital infection with syphilis. The lesion is painless and is characterized by a raised ulcerated surface

surrounded by a zone of induration. In some cases there is great œdema of the lip. The onset of the condition is soon followed by enlargement of the regional lymph glands, and in other respects the course is that of syphilitic lesions in other sites.

DISEASES OF THE FACE

Basal-cell Carcinoma (Rodent Ulcer)

The face is the commonest site of basal-cell carcinoma, and basal-cell carcinoma is the commonest tumour of the face. The tumour is usually situated near the medial or lateral palpebral commissure or in the naso-labial fold, less often in the frontal and temporal regions of the scalp.

At its inception the tumour lies deep to the epidermis and takes the form of a firm red pimple or flat, indurated plaque. At an early stage, or rarely after a considerable period, it breaks down, forming a rodent ulcer. Thereafter the growth spreads slowly, at first mainly at the expense of the surrounding integuments but later involving the deeper structures, and eventually it may attain large size and destroy a considerable part of the face. Despite its locally invasive character, the growth does not metastasize, unless, as sometimes happens, malignant change supervenes.

The general pathological features of basal-cell carcinoma are described in detail on p. 89.

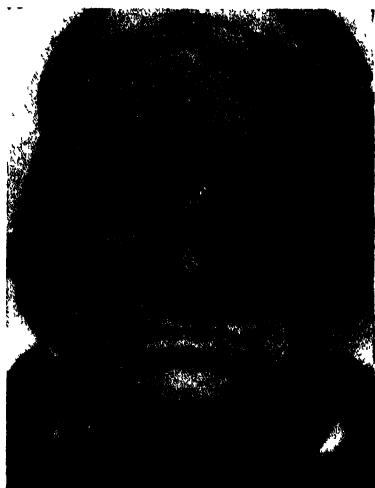


FIG. 173. Basal-cell carcinoma (rodent ulcer).

Squamous-cell Carcinoma (Epithelioma)

Squamous-cell carcinoma of the face is less common than the analogous growth on the lips and tongue, but it is by no means rare. The condition provides a notable illustration of the general concept of precancerous states, for it rarely occurs except upon a basis of some pre-existing focus of irritation or disease.

Lupus vulgaris provides one of the commonest predisposing agents, and lupus-carcinoma is a quite distinctive form of lesion. It is said to be commoner since the introduction of the X-ray treatment of lupus. The tumour is a typical squamous-cell carcinoma, but it differs from such tumours arising apart from lupus in its slow growth and comparatively low grade of malignancy. The tumour arises many years after the onset of lupus, and it may begin either where the lupus is active or where it is healed and replaced by fibrous tissue. Ulceration

occurs early, but the growth remains superficial for a long time with little induration of the deeper tissues. This slow spread is probably attributable to obliteration of lymph vessels consequent on the pre-existing disease, and indeed lupus-carcinoma does not spread to deeper tissues until it has extended superficially beyond the lupus area and has thus reached permeable lymph vessels. It then takes the usual course of skin carcinoma and metastasizes to regional lymph glands.

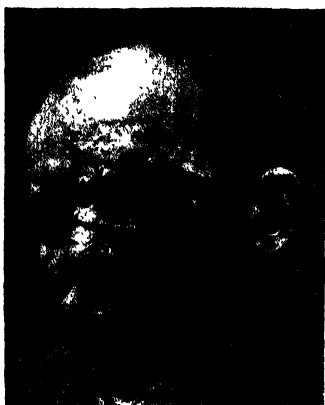


FIG. 174. Squamous-cell carcinoma arising in a rodent ulcer. An example of malignant change supervening on a comparatively non-malignant tumour.

(Museum of Royal College of Surgeons of Edinburgh.)

Basal-cell carcinoma is another lesion of the face that is liable to malignancy, though rarely. Sometimes the stimulus of inadequate irradiation by X-rays or radium has appeared to determine this change. In other cases long-continued irritation by carcinogenic paraffin products forms the predisposing factor, and in shale oil workers and mule spinners the face is a not uncommon site for skin carcinoma (*see* p. 69). Rarely a carcinoma has followed the irritation of tar

products, and a case has been reported in which carcinoma has occurred within a few months at a point burnt by a single spurt of hot tar.

DISEASES OF THE TONGUE

Leukoplakia (Chronic Superficial Glossitis)

This is a chronic affection of the tongue characterized by patchy heaping up of the epithelium with atrophy of the lingual papillæ and chronic inflammatory changes in the subjacent dermis. It is of importance as an intractable form of chronic hyperplasia which shows a definite tendency towards cancerous change.

The patches of leukoplakia vary in size, and, in extreme cases, may cover the greater part of the tongue. They usually begin near the lateral edge of the tongue in its anterior two-thirds, and spread thence on to the dorsum, or sometimes to the floor of the mouth. Rarely they occur on the lingual aspect of the cheek, and on the lips or gums.

In the affected area the mucous membrane is somewhat indurated, slightly raised above the general surface, and of a white or greyish-white colour, as though coated with paint. The lingual papillæ are flattened and atrophied, and may participate in the patchy whiteness. In advanced cases, a different appearance is sometimes seen. The superficial layer of the epidermis disappears, and the patchy whiteness gives place to a diffuse raw red appearance sometimes compared to raw beef. Often when the leukoplakia is extensive and of old standing the tongue becomes fissured.

Microscopically, there are pathological changes in both the dermis

and the epidermis. The dermis is the seat of a chronic inflammatory reaction, is unduly vascular and oedematous, and is infiltrated with small round cells of lymphocyte type.

The epidermis presents histological changes affecting any or all of its various cell layers. The most striking deviation from the normal is seen in the cells of the middle layers of the epidermis, which become swollen, vacuolated, and in some parts loaded with eleidin granules. In some cases there are collections of large hydropic cells, which somewhat resemble the characteristic cells of Paget's disease of the nipple (*see p. 386*). As a result of these changes in the middle layers the epidermis increases in thickness, and the interpapillary processes become broader and project more deeply towards the corium.

The superficial layer of the epidermis is generally increased in depth, keratinization is a prominent feature, and the superficial cells are extensively cornified. It is this feature that is responsible for the patchy whiteness of leukoplakia. In other cases, especially in the late stages of the disease, the superficial layers are reduced in depth or even absent.

The basal layer of the epidermis also shares in the proliferative changes of leukoplakia. The basal cells are hyperplastic, their nuclei are hyperchromatic and show some variability of size, and their cytoplasm is less granular and often somewhat swollen. In some cases, the basal cells present a degree of hyperplasia approximating to malignancy, and indeed the distinction between extensive leukoplakia and early malignancy is by no means easy.

In the late stages of leukoplakia, when the tongue presents the raw beef appearance, the microscopic features are different. The epidermis is now considerably thinned, and represented only by the basal cells, the superficial layers having been eroded. The basal cells are still more irregular in shape and size, and in their staining reactions they may show all the features of malignancy.

Etiology of Leukoplakia. Leukoplakia is rare before the age of thirty years, and is most common between the ages of forty and fifty years. It affects males far more often than females.

The Wassermann reaction is positive in more than 50% of cases, and



FIG. 175. Leukoplakia of the tongue. There is very considerable proliferation of the middle layer of the epidermis, with keratinization on the surface. The basal layer of cells is little affected.

it is generally believed that syphilis is an important predisposing cause.

Leukoplakia occurs most commonly in pipe smokers. It is not certain whether the heat of the tobacco smoke or the action of irritant combustion products is responsible.

In some cases irregular teeth or badly fitting dentures may be incriminated. Recent

observations suggest that the presence of multiple dental fillings composed of dissimilar metals may play a part in the ætiology, by setting up minute electrical currents when touched by the tongue. In this connexion it is interesting to note that Fitzwilliams has recorded a case of an electrician, who developed two small patches of leukoplakia, possibly due to repeated electrical stimulation when testing batteries by contact with the tongue.

Finally, it has been suggested that deficiency of vitamin A, which is known to im-



FIG. 176. Leukoplakia of the tongue. The basal layer of the epidermis is markedly hyperplastic. The more superficial layers are relatively unaffected. Note the extensive lymphocytic infiltration of the dermis.

pair the nutrition of epithelial tissues, may be an ætiological factor in some cases.

In regard to the significance of the pathological changes in leukoplakia, there are two main views. The commonly accepted view is that the primary change is proliferation affecting the basal cells of the epidermis, that the modifications in character of the superficial cells are secondary to this, and that the changes in the corium are of a reactive nature or due to superadded inflammatory processes.

The opposing view, which has been supported recently by Mekie, is that the initial lesion is a chronic inflammation, possibly toxic in origin, which primarily involves the subepithelial tissues, and later, as a result of œdema and vascular changes, affects the nutrition of the epidermis and leads to proliferative changes in that membrane.

Syphilis of the Tongue

The tongue may be affected by syphilis, either inherited or acquired. It is one of the commonest sites of extra-genital primary chancre, it regularly participates in the secondary manifestations, and it is often involved in lesions of the tertiary stage.

The **primary syphilitic lesion**, or chancre, results from a direct infection, and consequently it is commonest close to the tip of the tongue. The chancre forms a hard indolent nodule which ulcerates at an early stage and follows a course similar to that of primary chancres in other situations. It is accompanied by considerable enlargement and tenderness of the regional lymph glands in the submandibular and submental regions.

Secondary syphilitic lesions of the tongue usually take the form of mucous patches. They are most evident on the back and sides of the tongue, and are usually accompanied by similar lesions on the fauces, tonsils and palate.

Tertiary syphilitic lesions of the tongue are of especial surgical interest from their relation to carcinoma. Three distinct forms may be recognized: (1) chronic superficial glossitis (leukoplakia), (2) chronic parenchymatous glossitis, (3) gumma of the tongue.

(1) Chronic superficial glossitis in syphilis is characterized by changes in the superficial parts of the dermis and in the epidermis. An infiltration of round cells is succeeded by fibrosis in the dermis, and at the same time the epidermis presents the changes characteristic of leukoplakia.

(2) Chronic parenchymatous glossitis may be regarded as a diffuse gummatous infiltration of the tongue, and it is a common occurrence in tertiary syphilis. A similar but non-syphilitic glossitis may occur in a mercury stomatitis, and occasionally from other causes.

The essential pathological feature is an infiltration of the connective tissues and muscles by small round cells of lymphocyte type, which is followed by connective-tissue proliferation and, later, by fibrosis. In the early stages the tongue is swollen, and may be ulcerated. Later it becomes shrunken and distorted, lobulated like a cirrhotic liver, fissured and indurated.

(3) Gumma of the tongue occurs usually as a late tertiary phenomenon. It may be single or multiple. Multiple gummata are usually of small size and situated near the surface of the tongue, whereas a solitary gumma tends to attain greater dimensions and to arise more deeply.

A solitary gumma almost always lies in or close to the midline. At first it is deeply placed and forms a globular swelling of hard consistency. It increases in size somewhat rapidly, and later breaks down on the dorsal surface of the tongue, forming a chronic ulcer, deeply excavated, with hyperæmic, undermined or sharply cut margins and a yellow sloughing centre or base. A gumma is usually painless, and causes little interference with deglutition, mastication and articulation. The tongue may be protruded to the full extent and with no lateral deviation. The ulcer is surrounded by little or no induration in the substance of the tongue, and its edge, unlike that of a carcinoma, is not raised, rolled or thickened.

Carcinoma of the Tongue and Mouth

Carcinoma of the tongue is a new growth of common occurrence. In England and Wales it is responsible for approximately a thousand deaths annually. It occurs most often between the ages of forty-five

and sixty years, but is common at later ages, and is not unknown as early as the thirtieth year. Males are affected in 90% of cases, an incidence usually attributed to the greater frequency of syphilis and pipe smoking in this sex.

The predisposing factors in carcinoma of the tongue may be said to include all agents which result in an irritative hyperplasia of the mucous membrane. Syphilis is said to be present in from 50% to 80% of cases in which the dorsum of the tongue is involved. It probably exercises a predisposing influence through the fissuring, scarring and leukoplakia to which it gives rise. Non-syphilitic forms of leukoplakia



FIG. 177. Cancer of the tongue. Note the small ulcer and the raised, indurated margin. The tumour is unusually close to the mesial plane and has caused less fixation of the tongue than is usual.

(Museum of Royal College of Surgeons of Edinburgh)

precede the carcinoma in an appreciable proportion of cases. In other instances recurring trauma from sharp teeth or dentures, infection from pyorrhœa and irritation from hot tobacco smoke may be incriminated. It is noteworthy that carcinoma of the tongue is rare in the edentulous, and that it occurs usually at the side of the tongue where irregular teeth and the irritation of pipe smoking may be supposed to have the greatest effect. In certain parts of India the practice of chewing calcareous matter flavoured with betel nut is well known to predispose to cancer, and in other parts of the world tobacco chewing is said to have the

same effect. This form of cancer is especially apt to occur inside the cheek at the point where the bolus is lodged.

Site Affected. In most cases the carcinoma arises at or near the edge of the tongue in its anterior two-thirds, or at a corresponding level in the floor of the mouth. Carcinoma near the midline of the tongue is uncommon, and almost invariably secondary to a syphilitic lesion. The tip of the tongue is rarely involved. Carcinoma in the posterior part of the tongue occurs commonly at the side close to the glosso-palatine arch. The posterior part of the tongue may be invaded by carcinoma of the epiglottis and pharynx.

Naked-eye Appearance. The appearance of the growth is usually characteristic, and such atypical forms as are described are rare. In its early stages the growth may take the form of a hard submucous nodule (nodular type), a large, red, projecting papillomatous mass (papillary type), or a deep fissure with indurated margins (fissured type). In the majority of cases, however, whatever the manner of its origin, the growth rapidly breaks down and forms a malignant ulcer (ulcerative type). Such an ulcer on the tongue has a highly characteristic appearance. The actual crater is not necessarily deep, and may

be of small size. The floor of the ulcer is of irregular shape, and is surrounded by a broad margin, which is raised, nodular and everted. The base of the growth and the adjacent substance of the tongue are indurated and of stony hardness.

Rarely the tumour does not ulcerate, but spreads deeply and infiltrates the root of the tongue, causing it to become indurated, puckered and shrunken (wooden tongue).

Microscopic Appearance. In the great majority of cases the growth is a squamous-cell carcinoma (epithelioma). Carcinoma of basal-cell type occurs less commonly. Adeno-carcinoma has been described, but is extremely rare. The ordinary squamous-cell carcinoma has the characteristics common to tumours of this type, and consists of clubbed or flask-shaped processes of epidermis which grow down into the subjacent stroma and muscle. The majority of the cells are of the character of prickle cells. According to the degree of malignancy there are varying degrees of anaplasia, and in the more rapidly growing tumours mitotic figures are numerous. Cell nests are sometimes present but are not invariable.

Effects. The malignant ulcer is prone to bleed and liable to gross secondary infection, and such complications bring the patient to a state of anæmia and cachexia. The breath is foul and fætid. Infiltration of the muscles leads to fixation of the tongue and to interference with articulation and deglutition. The tongue is protruded with difficulty, and tends to deviate towards the affected side. Salivation is increased, and since deglutition is painful saliva dribbles from the mouth.

Pain is an early symptom, and may be so severe as to interfere with sleep. At first the pain is limited to the affected region, but later it radiates through the tongue, and eventually, by reflex involvement of the chorda tympani and the auriculo-temporal branch of the trigeminal, it is referred to the ear and the side of the face and head.

Spread. A carcinoma of the tongue spreads locally and invades regional lymph glands. The floor of the mouth and the muscles at the base of the tongue are involved early, and if the tumour is situated far back it may spread to the tonsil, the palatine arches and the palate. The lymph glands involved first are usually those of the submandibular (submaxillary) group. The submaxillary salivary gland frequently escapes. The glands of the upper deep cervical group are generally involved later, but sometimes they may be the first to be obviously



FIG. 178. Carcinoma of the tongue. The growth has originated at the under surface of the tongue and has infiltrated the floor of the mouth and the mandible.

(Museum of Royal College of Surgeons of Edinburgh.)

enlarged, especially from a growth in the posterior part of the tongue. From the tip of the tongue the submental glands are often involved at an early stage.

Spread to distant situations such as the mediastinal lymph glands, the liver and the lungs is uncommon, except in the later stages, and death is usually the result of such local complications as hæmorrhage, infection and bronchopneumonia.

Rare Tumours of the Tongue

Occasionally the tongue becomes the seat of sarcoma. In the majority of cases it is a lymphosarcoma derived from the lymphoid tissue on the posterior third of the tongue. The tongue may be involved in lymphosarcoma derived from the tonsil. Rarely a spindle-cell and mixed-cell sarcoma occurs. Such tumours present no special characteristics. They form soft rounded masses, which grow rapidly and are prone to hæmorrhage and infection. Metastases may occur in distant situations, but usually death is due to sepsis or hæmorrhage from the vascular tumour.

Other rare tumours of the tongue include lymphangioma, cavernous angioma, papilloma, fibroma, lipoma, osteoma, rhabdomyoma, mixed tumours and ectopic thyroid enlargements (*see p. 416*).

Cancer of the Floor of the Mouth

Cancer of the floor of the mouth is a common condition. It may be due to an extension from a cancer of the tongue, or it may arise primarily. In its general characters it resembles lingual cancer, and usually forms a hard craggy ulcer. Most commonly it is situated to the lateral side of the anterior part of the tongue, and from this region it rapidly infiltrates the muscles of the floor of the mouth, the gum, and alveolus, and spreads to the regional lymph glands of the submandibular region. The tongue is fixed and can be protruded only with difficulty. Salivation is increased and severe pain is experienced both in the growth itself and in the tongue, and referred to the side of the head.

Tumours of the Palate

The commonest tumour of the palate is the *squamous-cell carcinoma* (epithelioma), and it may originate in this situation or spread thither from the alveolus or cheek. It forms an ulcerating tumour which has the general characteristics of such growths and spreads slowly, involving neighbouring tissues and metastasizing to regional lymph glands.

A *sarcoma* affecting the palate usually originates in the maxilla in the region of the antrum.

Mixed-cell tumours occur in young subjects, and are similar in structure to salivary gland tumours. In some cases striped muscle fibres have been present (rhabdomyoma). Such tumours vary greatly in malignancy, but usually they are of rapid growth.

Endothelioma, *adenoma* and *papilloma* are extremely rare.

CYSTIC SWELLINGS OF THE MOUTH

Small retention cysts may occur in the mucous glands of the lips and cheeks, and if they are situated near the teeth they may become abraded and ulcerated. Cysts of a similar nature may also occur along the edges of the tongue and in the glands (of Blandin and Nuhn), situated beneath the tip of the tongue.

These cysts are of a bluish-grey colour, small in size, very thin walled and well circumscribed. Their contents are thin, clear and jelly like.

Ranula. This is a conglomerate term applied to cystic swellings in the floor of the mouth. The exact nature and origin of some of these cysts are not entirely established.

The cyst is usually unilateral, but it may be bilateral. It generally appears in childhood, and grows slowly. It is bluish-grey in colour and situated at the side of the frenum. The mucous membrane over the cyst is thin but movable. The tongue is raised to a variable extent according to the size of the mass, which may be several centimetres in diameter. Sometimes the cyst extends behind the mylohyoid muscle and causes bulging in the neck behind the submaxillary gland. The duct of the submaxillary salivary gland is separate from the cyst. Occasionally a cystic tumour of the floor of the mouth has a communication with a cyst in the neck, and pressure on the oral swelling increases the size of that in the neck. A large cyst of long standing may cause pressure atrophy or maldevelopment of the lower jaw.

Histological examination of a ranula shows that in some cases it is lined with columnar or cuboidal epithelium, in others with fibrous tissue alone, probably as a result of destruction of the epithelial lining. In a few instances the epithelium is ciliated. The cysts are filled with clear or jelly-like fluid containing mucin, but no salivary ferment.

The origin of these cysts is uncertain. They have been regarded as dilatations of the ducts of the submaxillary or sublingual salivary glands, as distension cysts of hypothetical bursæ or as retention cysts of the mucus-secreting glands of the sublingual mucous membrane.

There is anatomical evidence to suggest that some of the cysts are of branchial origin and are due to prolongation forward of an unobliterated portion of the cervical sinus. It has been claimed that some of the cysts communicate with a cyst in the neck, or have a fibrous extension into the submaxillary region.

Dermoid Cysts of the Floor of the Mouth. A dermoid cyst of the floor of the mouth is of developmental origin, and is due to the inclusion of ectoderm at the time of coalescence of the two halves of the mandible. The cyst is therefore usually situated in the middle line; it lies behind the symphysis menti and between it and the hyoid bone, to either of which it may be adherent. When large, the cyst presents in the floor of the mouth and in the submental region. As growth proceeds it may deviate towards one side. When large, it may interfere with deglutition or even respiration, and the tongue may protrude. Although of developmental origin, the cyst is rarely evident before puberty.

The wall of the cyst is composed of fibrous tissue, and is lined with

squamous epithelium in which sweat glands and hair follicles may be present. Sebaceous glands secrete the cheesy material that fills the cavity. In appearance the cyst is yellowish, smooth and spherical; it may pit on pressure, unless its contents are very firm.

Thyroglossal Cysts in the Tongue. The suprahyoid portion of the thyroglossal duct may undergo cystic dilatation, though much less commonly than the infrahyoid portion (*see* p. 417). The cyst generally appears in childhood or adolescence, and slowly increases in size. It is situated in the line of the thyroglossal duct, that is, in the midline between the foramen cæcum and the mid part of the hyoid bone. When the cyst arises in the upper part of the duct it projects upon the dorsal surface of the tongue in its posterior third, and in this situation it may interfere with deglutition and may even embarrass respiration. When the cyst arises in the lower part of the duct above the hyoid bone it tends to project at the floor of the mouth in front of the tongue, and in this situation it is liable to be mistaken for a dermoid cyst. Formerly such a cyst was classed as a dermoid under the title *tubulo-dermoid cyst*.

TUMOURS OF THE JAWS

The jaws are subject to the same types of tumours as other bones, and they are also liable to be affected by tumours of the gums (epulis) and by tumours arising in connexion with the teeth (odontoma). There are considerable variations in the incidence of the various types in the maxilla and mandible respectively.

Tumours of the Maxilla. Carcinoma is now regarded as the commonest tumour affecting the maxilla. The growth may start in the mucous membrane of the nostril or of the hard palate, and invade the bone secondarily, or it may arise primarily within the maxillary antrum. Carcinoma of the antrum is of variable character. Sometimes the cells are columnar in shape, and an ill-defined adenomatous structure may be present. In other cases the cells are undifferentiated, and the appearance closely resembles that of a sarcoma.

Carcinoma of the maxilla is locally very malignant. It invades the bone in all directions and may involve the palate, the contents of the orbit and the naso-pharynx. It rarely disseminates to glands or distant viscera until a late stage.

Giant-cell tumour of the maxilla is not uncommon. It grows slowly, "expanding" the bone, and is generally of benign character. In its pathological features it resembles giant-cell tumours of other bones (*see* p. 160).

Sarcoma of the maxilla is now believed to be considerably less common than carcinoma. It may arise near the posterior aspect of the maxilla close to the speno-maxillary fossa, from the anterior aspect under the cheek, or from the region of the antrum. According to its position the growth may invade the orbit and displace the eyeball, or it may project under the cheek or ulcerate into the nasal cavity. Simple tumours of the maxilla are rare, apart from epulides and odontomes, which will be described separately below. Fibroma, chondroma and osteoma may occur.

Tumours of the Mandible. Apart from odontomes, the commonest

tumour of the mandible is a carcinoma invading the bone from the gum or the floor of the mouth.

Giant-cell tumour is not uncommon. It occurs most often in young adults, and generally affects the body of the mandible. The tumour grows slowly, and may attain considerable size. It "expands" the bone, so that the soft vascular tumour retains a thin osseous shell, and may give a characteristic crackling sensation on palpation.

Sarcoma is a rare tumour in the mandible. It is generally of spindle-cell type, grows rapidly and is highly malignant.

Epulis

Epulis is a clinical term applied to tumours which grow from the alveolar processes of the jaws. There are two pathological types—the fibrous and the giant-cell epulis.

The fibrous type is the more common. It arises from the edge of the gum at the neck of one of the incisor or premolar teeth. The tumour is firm, has a smooth surface, is covered by normal mucous membrane, and is often pedunculated. It grows slowly but may eventually be 3 or 4 cm. in its long axis; it may grow between the teeth and loosen them.

A fibrous epulis grows from the periosteum or from the periodontal membrane, and chronic inflammatory conditions of the gums are said to favour its development. It is a fibroma, and is composed of loosely arranged spindle cells which surround numerous blood vessels or thin-walled vascular channels. Myxomatous degeneration is not uncommon. Round cells and giant cells of the foreign-body type are usually present in the tumour. Certain of the growths are very vascular, and have an angiomatous appearance. They are soft and spongy, bluish-red in colour, and grow more rapidly than the common fibrous type.

The giant-cell type grows more rapidly than the fibrous epulis. It is usually sessile, and forms a smooth, soft lobulated mass, covered by dark red or purple mucous membrane. The tumour usually begins in the interior of the alveolus and, as it increases in size, tends to project beneath the gums; it frequently causes loosening of one or more of the teeth. In the mandible the tumour may extend into the body of the bone, producing a cyst-like structure surrounded by a shell of bone. Microscopically, the tumour is composed of giant cells of foreign-body type in a vascular stroma of fibrous tissue.

A giant-cell epulis is a benign tumour, but wide excision is required to prevent its recurrence.

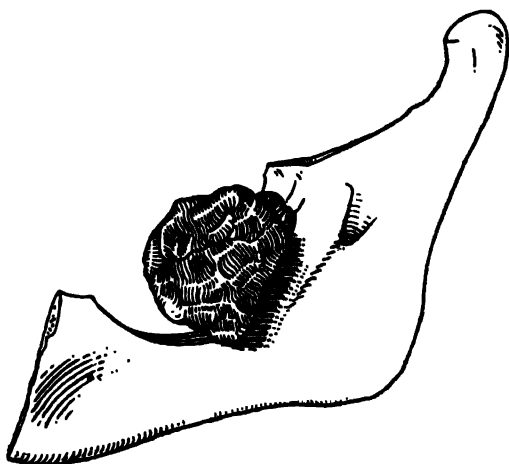


FIG. 179. Epulis of giant-cell type.
(Museum of Royal College of Surgeons of Edinburgh.)

TUMOURS AND CYSTS OF DENTAL ORIGIN—ODONTOMA

An odontome is a tumour derived from the tissues—ectodermal and mesenchymal—concerned in the development of the teeth, and their pathological characters depend on the stage of development of the embryonic dental elements when abnormal growth begins. With few exceptions the tumours are benign, but they may simulate malignant tumours.

Some of the tumours that have been included under the heading of odontoma are not true neoplasms, but are merely inflammatory overgrowths of the tissues around an unerupted tooth.

The classification of dental tumours formulated by the British Dental Association is comprehensive, and forms a convenient basis for description of the various types. It is as follows :—

A. Epithelial Odontome : (a) Dental cyst, (b) Multilocular cystic tumour, and (c) Dentigerous or follicular odontome.

B. Composite Odontome.

C. Connective Tissue Odontome : (a) Fibrous, (b) Cementomatous.

Development of the Teeth. Knowledge of the processes involved in the development of the teeth is necessary for a correct appreciation of the mode of origin of dental tumours.

In embryos the first change which foreshadows the development of teeth is the appearance of a ridge of epithelium along the line of the gum ; this epithelial thickening is known as the *common dental rudiment*, and multiplication of its deeper cells at intervals causes a series of epithelial projections in the mesodermal tissues. The tip of each projection becomes cup-shaped from the protrusion into it of a process of mesodermal tissue. The epithelial cup and the mesodermal projection constitute a *dental papilla*, which becomes separated from the dental ridge. Normally, ten dental papillæ develop in each jaw to form the “milk teeth” ; later, however, other papillæ develop to form the second molars of the first dentition, and three other papillæ appear, which represent the future permanent molars. The other permanent teeth are developed from a second series of papillæ.

The cells at the summit of the mesenchymal papilla assume a columnar form and are known as odontoblasts ; they give rise to dentine. The epithelial cap which covers the mesenchymal papilla becomes the *enamel organ*, which becomes differentiated into three layers of cells—flattened, stellate, and columnar—from without inwards. The columnar cells—*enameloblasts*, are the active elements in producing enamel.

Each developing tooth is surrounded by a vascular fibrous tissue membrane, the *dental sac*, and the mesenchymal papilla, enamel organ, and the dental sac form together the so-called *tooth follicle*.

The cement which covers the dentine of the roots of the teeth is formed from the mesenchymal tissues in the same way as membranous bone.

Tumours of dental origin may arise in the following ways : (1) From proliferation of groups of cells, derived from the common dental rudiment or from the enamel organ, that may be scattered about the

teeth in infancy or even in adult life. Such groups of cells were originally demonstrated by Malassez, and are known as "débris epitheliaux paradentaires." (2) From disorderly proliferation of the cells of a dental follicle. (3) From excessive production of dental follicles.

Epithelial Odontome

(a) **Dental Cyst** (Radiculo-dental cyst). This type of cyst occurs in later adult life and usually develops in connexion with a pulpless tooth, especially one of the incisors or the canines of the upper jaw. It arises from paradental epithelial rests, which are probably stimulated to proliferate by infection. The cyst is unilocular, is attached to the fang of a tooth, and is usually small, although it occasionally grows to enormous size and often extends into the maxillary air sinus and causes bulging of the cheek. A portion or the whole of the affected tooth may lie within the cavity of the cyst, but the tooth and the cyst are sometimes quite separate. Occasionally there are multiple cysts, and they may fuse (see Fig. 180).



FIG. 180. Large dental cyst.
(Museum of Royal College of Surgeons of Edinburgh.)

A dental cyst is lined with squamous epithelium and therefore it may be mistaken for a dermoid; very rarely the epithelium is columnar, indicating more emphatically its dental origin. If infected the epithelial lining may be almost completely destroyed and then the walls are fibrous. The contents of the cyst are serous or mucoid, and cholesterol crystals may be present.

(b) **Multilocular Cystic Tumour** (Adamantinoma or enamel-cell tumour). This tumour occurs most often in early adult life, but it has been found in childhood and in old age. The mandible is affected much more frequently than the maxilla (11 : 1), and the region of the angle is the usual starting point. The tumour is usually simple and grows very slowly, and in the absence of complication, such as infection, is quite painless. Very occasionally the tumour has given rise to metastases in other bones. In exceptional cases tumours of this type have appeared to arise primarily in the tibia and other long bones.

The tumour may be solid or cystic; it has a lobulated surface and thin walls. It causes enlargement of the alveolar border of the jaw, usually more on the outer than on the lingual aspect. From expansion and thinning of the bone, "egg-shell crackling" may be detected, and neighbouring teeth may be loosened and displaced. Large tumours in the upper jaw usually encroach upon the maxillary air sinus and may even extend to the orbit or to the naso-pharynx. Ulceration and infection within the tumour may modify its appearance.

An enamel-cell tumour has an external bony wall enclosing a solid, or more often a cystic, growth. The cysts are multiple and are filled with yellow or reddish mucoid fluid; the walls of the cysts may be smooth or lined with papillary projections. The remainder of the tumour is composed of fibrous or of bony trabeculae in varying proportions.



FIG. 181. Epithelial odontome. The cells of basal type lining the cysts correspond to enameloblasts. They swell, become loosened towards the centre, and ultimately liquefy, thus giving rise to cyst formation.

The solid parts of the tumour may resemble a carcinoma, and in some specimens the connective tissue undergoes such overgrowth that it may resemble a sarcoma. Gritty particles of imperfectly formed enamel may be present.

Microscopically, the epithelial elements in these tumours are very variable in form, and the appearances may differ in various parts of one tumour. Three types are described which, however, have not a sharp dividing line: (1) the squamous-cell type, which shows cords of squamous cells with intercellular fibrils and cell nests, and, in addition, isolated foci of columnar enameloblasts; (2) the plexiform type, composed of convoluted columns of epithelium surrounded by a dense or cellular fibrous stroma; the epithelial cells show no tendency to flattening; (3) the glandular type, composed of columnar enameloblasts, which may be arranged in many different ways.

In all types the stroma may be dense—hyaline, myxomatous, or cellular.

This type of odontome is believed to arise from cells of the primitive enamel organ, but by some it is considered to originate from the paradental epithelial *débris*. It is at least certain that it is of epithelial origin.

(c) **Dentigerous Cyst** (Follicular odontome, odontocèle). This type occurs in young adults during or after the second dentition; it is more common in the lower than in the upper jaw. At the site of the cyst a tooth, usually a canine, an incisor, or a premolar, is missing. The cyst grows slowly and causes a globular enlargement of the alveolus. Adjacent teeth may be loosened and displaced. Inside the cyst there is an unerupted tooth which usually protrudes from the base of the cavity, but may lie free. The wall of the cyst is usually attached at the neck of the tooth, and the root of the tooth is loosely buried in the jaw. The cement, dentine, and the root of the tooth are generally very imperfectly developed. Squamous epithelium usually lines the cyst, but occasionally cubical epithelium is present. The

fluid in the cyst is glairy and contains cholesterol and broken-down epithelial cells.

The origin of a dentigerous cyst is uncertain. It is generally supposed that it arises from dilatation of the dental follicle, but as the tooth within the cyst lacks dental cuticle (Nasmyth's membrane), it has been suggested that it arises from degenerative changes in the enamel organ at an early stage of its development.

Composite Odontome

This type of tumour probably arises from disordered growth of the whole tooth germ, which results in an irregular conglomeration of dental tissues with little or no resemblance to a tooth. It occurs in young subjects before the age of twenty-five years and is almost always situated in the mandible. At the site of the tumour one or more teeth, especially the molars, are absent.

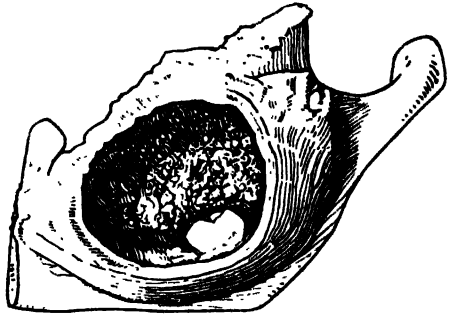


FIG. 182. Left half of mandible of an adult showing a follicular odontome. The unerupted tooth is a third molar.

(Museum of Royal College of Surgeons of Edinburgh)

The tumour is hard and irregular, and lies within the jaw; it may erupt like a normal tooth and this may predispose to infection and lead to extrusion of the tumour.

Another variety of composite odontome consists of a conglomeration of imperfectly developed teeth (denticles) surrounded by a fibrous capsule lined by squamous epithelium. The teeth show variable quantities of enamel, dentine, cement, and pulp. The dividing line between this type of cyst and a dentigerous cyst is not very definite.

The mode of origin of a composite odontome is rather obscure. Some believe that it is due to misplacement of tooth follicles in early life, others that it is due to proliferation of paradental epithelium (Malassez). Ewing considered that the absence of one or more teeth in this type of tumour indicates that all the primitive dental structures—epithelial and fibrous—are concerned in the production of the tumour, and that, when there are denticles, there has been an over-production of dental follicles. Ewing found it difficult to conceive these tumours as arising from paradental *débris* because of the orderly and active growth.

Connective Tissue Odontome

A fibrous odontome is exceedingly rare. It is probably not a tumour, but an overgrowth of fibrous tissue around an unerupted tooth. Rickets is believed to predispose to its development, as most examples have been found in children who have suffered from this disorder.

Calcification and ossification may occur in the walls of a fibrous odontome giving rise to a *cementoma*.

DISEASES OF THE SALIVARY GLANDS

Pyogenic Infections

Acute pyogenic inflammation of the salivary glands is practically confined to the parotid and it usually terminates in suppuration—*suppurative parotitis*. The condition is most common in adults as a complication after operation, but it may occur in acute febrile illnesses, especially pneumonia and typhoid. It commonly occurs in debilitated persons, and often heralds the fatal issue. The onset is usually sudden, with pain and swelling in one parotid gland, and the signs and symptoms of a severe infection. Not infrequently both parotid glands are affected, simultaneously or in succession.

Ætiology. Dryness and uncleanness of the mouth and the diminished secretion of saliva with which these are associated are the most important predisposing factors. The dryness of the mouth is usually due to dehydration or to lack of the normal stimuli to salivation. Thus the disease very often complicates operations on the abdomen in which fluid by the mouth has been greatly restricted. Infection reaches the gland by the salivary ducts, and the organisms usually present are staphylococci and pneumococci, less often streptococci and diphtheroids. The absence of mucin from the saliva of the parotid gland is believed to favour infection.

Morbid Anatomy. The infection is multicentric and is characterized by multiple points of necrosis scattered throughout the gland; later small foci of suppuration develop and eventually may become confluent, forming an abscess which may rupture externally. The early necrosis, comparable to that of a carbuncle, may be attributed partly to the necrotoxic action of the common causative organism, staphylococcus aureus, and partly to the fact that the inflammatory products are confined under tension within the dense parotid fascia. The orifice of the parotid duct is swollen and red, and cloudy or purulent saliva may be expressed from it. In some cases the disease is very severe and is associated with cellulitis of the neck, head, and face. For a long time the pus remains confined within the capsule; later it may burst through the fascia and rupture into the external auditory meatus or point below the angle of the jaw. In untreated cases the pus may burrow into the retropharyngeal space or invade the temporo-mandibular joint. Both are rare occurrences.

Salivary Calculus—Sialolithiasis

Calculi are most common in the duct of the submaxillary gland; they are much less common in the parotid duct, probably because the secretion of the parotid gland is less viscid and poorer in salts.

The calculus, which resembles dental tartar, is composed principally of the phosphate and carbonate of lime, with a small percentage of organic matter. Probably they are formed as a result of infection, and are due to the deposition of inorganic calcium salts upon nuclei consisting of mucus, degenerated epithelium and bacteria. On rare occasions a foreign body, such as a piece of straw, a fruit seed, or mycelia of actinomyces, may form a nucleus for stone formation.)

A salivary calculus is usually single, brown or grey in colour, and slightly rough on the surface. It may be no larger than a pea, but often

it is fusiform and about the size of a date stone. In the rare cases in which two or more calculi are present they may become eburnated at their points of contact and appear to be fragments of a fractured stone.

The chief effect of a salivary calculus is to cause retention of salivary secretion, and this is usually associated with periodic swelling and pain in the salivary gland, particularly at meal times, sometimes aggravated by infection. If obstruction becomes complete retention cysts may develop. As a result of continued exacerbations of inflammation the stone may lie in a bed of granulation tissue or of cicatricial tissue, and the indurated mass may be mistaken for a tumour of the floor of the mouth. In rare cases, the calculus erupts through the wall of the duct, and, in the case of the parotid, this may lead to an external fistula.

In the submaxillary gland, multiple calculi occasionally are present in the smaller ducts, and they may lead to chronic enlargement or to suppuration within the gland.

Chronic Enlargement of the Salivary Glands

As a result of infection from the mouth, sometimes following a dental extraction, one of the salivary glands may become enlarged, swollen and tender. The parotid gland is usually affected, and, at first, the inflammation is mild and subsides. Recurrence of inflammation is usual, either at short or long intervals, until finally the glandular enlargement persists and other groups of glands become involved. The affected gland is the seat of chronic inflammatory changes and its duct is dilated and the seat of exfoliation. Salivary secretion is reduced, its digestive properties impaired, and the infective character of the disease is borne out by the finding of leucocytes, epithelial casts and organisms in the turbid saliva from the affected gland.

Lymphomatous Enlargement (Mikulicz Disease). This syndrome represents the final picture of a progressive disease, the earlier phases of which may not be identified so clearly. It generally affects adult males, and leads to great disfigurement. The secretion of saliva is reduced and dryness of the mouth (xerostomia) is complained of, and conjunctivitis and pharyngitis may co-exist.

The lacrimal glands are enlarged first, and only later the salivary glands. The mucous glands in the tongue and cheek may also become enlarged. The extent of the affection varies in different cases, for it may be found that the lacrimal glands alone are involved, or that the salivary glands are affected in various degrees. The ætiology of the glandular enlargement is unknown. No bacteria have been demonstrated, and there is no evidence that it is due to infection from the mouth or the conjunctiva. There is a syphilitic history in a few, but it is probably no more than a coincidence.

Histological examination shows that there is a generalized lymphocytic infiltration, and there may be complete lymph follicles with germ centres. The glandular tissue is reduced in amount but shows no primary disease.

Sometimes the condition is accompanied by either local or general hyperplasia of lymphoid tissue, and sometimes there is a relative or

actual increase of lymphocytes in the blood. In others, there is true leukæmia with enlargement of the spleen, etc.

Uveo-parotitis. This is as yet an indeterminate entity, in which there is an association of inflammatory lesions of the uveal tract and of the parotid and sometimes other salivary glands.

The enlargement of the parotid gland appears abruptly and may be attended by fever; it is either preceded, or followed by irido-cyclitis. In a large proportion of the cases unilateral or bilateral facial paralysis develops and persists for a variable time. There may be temporary paralysis of other nerves. In many cases skin eruptions of a tuberculide type are present.

The swelling of the affected salivary gland is firm, nodular and painless. It is the seat of fibrous tissue proliferation, and microscopically, in most cases, there is separation of the glandular acini as a result of infiltration by lymphocytes and giant-cell aggregations resembling tubercles.

The ætiology of uveo-parotitis is obscure. Formerly it was regarded as tuberculous, but there is good reason to believe that in many cases, if not all, it occurs as one of the manifestations of Boeck's sarcoidosis (p. 260).

The disease occurs most often in women, especially in the second and third decades. It pursues a chronic course, lasting for weeks or months. Recovery is generally complete, but there may be relapses. There may be residual ocular defects as a result of synechia and keratitis.

Tumours of the Salivary Glands

Tumours of the salivary glands usually occur in adults after the age of thirty years. Usually they grow slowly and remain localized; less often they proceed rapidly and assume malignant characters. They may extend rapidly by infiltration and may metastasize to the lymph glands in the neck, though seldom by the blood stream. The parotid gland is affected in the majority of cases (90%), the submaxillary gland only rarely, and the sublingual gland still less often. Similar tumours may arise occasionally in the lips and cheek, the nares, the lacrimal gland, and the hard and soft palate.

The common type of tumour has a mixed structure of cellular elements, myxomatous and fibrous tissue. It may be firm and hard and well encapsuled, showing only slight tendency to recurrence after removal. The more cellular types are softer and more diffuse, and may have a deficient capsule and show a greater inclination to recur after operation.

Recurrence after removal is a special character of salivary gland tumours, it takes place in at least 20%, either soon after operation or many years later. Generally recurring tumours are of the same structure as the original one and do not show any greater tendency to malignancy.

Histologically, the most notable feature of the tumours is their mixed structure, and the great variability in different tumours has been responsible in the past for the catalogue of descriptive names applied to

them. It is more accurate to regard them as "mixed tumours," subject to variations in their cellular differentiation and the extent to which myxomatous tissue may be present. A typical example shows collections of cells and myxomatous tissue enclosed within a well-developed fibrous capsule. The cells show various forms—spheroidal, cuboidal, spindle, or even squamous, with a small, darkly staining, angular nucleus. When myxomatous tissue is present it lies in juxtaposition to the cellular components, from which it is probably derived. More detailed examination shows that in many parts of the tumour the cells are arranged in irregular masses or branching columns; but usually there are vague or definite duct or alveolar formations suggesting a reproduction of the normal gland structure. Thus, taking into account the common variations from the standard pattern, there are types which may be regarded as an adenoma, types, more cellular and with less differentiation, which might be classified as either adeno-carcinoma or sarcoma. Mitosis and irregular proliferation (rather than the cellularity of the tumour) form the most reliable criterion of malignancy.

The origin of salivary gland tumours is an academic problem. Their common epithelial ancestry is suggested by the gradations in differentiation present in various examples; in one there may be little but myxomatous tissue, in another well-formed tubule formations, and in many merely suggestions of genuine epithelial origin.

A recurring controversy is that of the origin of myxomatous (or mucoid) tissue within the tumours. It has the appearance of cartilage in stained secretions, but more specific stains suggest it is due to degeneration or is a derivative of the cellular components (or possibly the stroma), rather than an accidental inclusion such as would suggest a branchio-genetic sequestration in the territory of the salivary glands. Such mucoid tissue is not uncommon in other tumours, *e.g.*, sebaceous adenomata and tumours of the testis, and can be interpreted, as in these examples, as a cellular by-product rather than an independent tissue formation.



FIG. 183. Mixed tumour of the parotid gland. The cells are arranged irregularly, but in places there is evidence of tubule formation. A large amount of mucoid tissue lies between the masses of epithelial cells.

(Laboratory of Royal College of Physicians of Edinburgh.)

Adenolymphoma of the Salivary Glands

This rare tumour occurs in late adult life, especially in the parotid gland in the preauricular region or at the angle of the mandible. It is a simple readily enucleable tumour seldom reaching a size greater than a walnut. It may be solid but is more often cystic and contains mucoid or turbid fluid. Microscopically it consists of columnar epithelium supported by a lymphoid stroma with active germ centres. The solid portions of the tumour may be composed of gland acini.

It is believed that the tumour is derived from ectopic salivary gland epithelium within lymphoid tissue.

BRANCHIAL CYSTS AND FISTULÆ

A branchial cyst is of developmental origin and takes origin from persisting remnants of the cervical sinus—the ectoderm-lined space which is formed by the second branchial arch as it overgrows the more caudal arches.

A branchial cyst forms a rounded tense swelling below and behind the angle of the jaw; it usually occurs in early adult life and is often mistaken for a tuberculous gland. The cyst has fibrous walls and is seldom larger than a golf ball; it lies deep to the cervical fascia and is partly covered by the sterno-mastoid muscle. It is in contact with the carotid sheath, and a prolongation of the cyst may bulge between the internal and the external carotid artery; usually the accessory nerve is immediately posterior to the upper part of the cyst. The lining membrane of a branchial cyst is squamous epithelium, which generally shows keratinization; a variable amount of lymphoid tissue is usually present in and around the cyst wall. The contents consist of glairy, mucoid fluid which generally holds in suspension a large number of cholesterol crystals and desquamated epithelium. The discovery of cholesterol crystals on aspiration of the cyst is a valuable diagnostic sign.

The cyst may be the seat of recurrent attacks of inflammation, and in rare instances suppuration occurs. A persistent sinus may result from incision of the cyst. It is doubtful if a carcinomatous change ever occurs in the lining epithelium.

In rare instances a small deeply seated cyst is found at autopsy attached to the external surface of the pharynx. This variety of cyst is lined by columnar epithelium, which may be ciliated. The cyst rarely gives rise to signs or symptoms unless it becomes infected; it is believed to originate from the mucous membrane of one of the primitive pharyngeal clefts.

A *branchial fistula* or *lateral fistula of the neck* is a blind track which extends upwards from the skin surface of the neck deeply towards the pharynx. The orifice of the sinus is usually situated at the anterior border of the sterno-mastoid muscle about 4 to 6 cm. above the sterno-clavicular joint. The sinus may remain permanently open and discharge a little serous fluid, or it may be closed for long periods.

The fistulous tract forms a cord-like structure with a small, slightly tortuous, irregular lumen. It is lined with several layers of columnar

epithelium which is generally ciliated, but sometimes shows squamous metaplasia. A large amount of lymphoid tissue is present in its walls. When traced upwards the fistula is found to sink gradually through the superficial fascia and the platysma, and at the upper border of the thyroid cartilage it pierces the deep fascia. In its further course it lies superficial to the internal carotid artery and the glosso-pharyngeal nerve, but deep to the lingual, occipital, and external carotid arteries. It is crossed by the hypoglossal nerve and the stylomandibular ligament. The fistulous tract ends in the region of the supratonsillar fossa. It is believed that originally a membrane separated the fistula from the pharynx. In cases seen surgically, however, the fistula may communicate with the pharynx.

A branchial fistula is generally regarded as due to persistence of the *cervical sinus*, the ectoderm-lined track corresponding to the second branchial cleft. This view fails to account for the character of the lining membrane of the fistula, which is usually of ciliated columnar character. An alternative theory, which seems more plausible, attributes the fistula to persistence of the thymo-pharyngeal duct.

Branchiogenetic carcinoma has been described. The tumour is a squamous-cell carcinoma of horny type, very hard and indurated, and sometimes partly cystic. It arises deeply in the neck, in close relation to the carotid vessels, and infiltrates widely at an early stage. The microscopic appearance of such tumours is very diverse and the cells may resemble those of a carcinoma or of a sarcoma; most often they are "prickle cell" type. A feature which is generally held to signify the branchiogenetic origin of the tumour is the layer of lymphocytic tissue which encapsules the tumour. Nodules of cartilage may occur in the tumour.

While this is the description applied to branchiogenetic carcinoma, it must be emphasized that the branchial origin of such tumours is difficult of proof. In some cases, doubtless, tumours of this character are actually secondary growths, from a primary focus in the nose, pharynx, Eustachian tube, larynx, accessory air sinuses or thyroid gland.

TUMOURS OF THE CAROTID BODY (*Paraganglioma* : *Perithelioma*)

The carotid body is situated either in the bifurcation of the common carotid artery or on the posterior surface of the internal carotid artery. It is developed from embryonic ganglion cells of the sympathetic nervous system. Normally, it is composed of polyhedral cells collected into spherical clumps or nodules. Some of the cells stain dark brown with chromic acid (chromophil), like those of the suprarenal medulla, but they do not contain adrenalin. The gland normally contains a few nerve ganglia and non-medullated nerve fibres. It is very vascular and is supplied by a special arteriole and venule.

Tumours of the carotid body are rare. They appear most often about puberty and give rise to a protruding swelling in the neck.

The tumour may attain the size of a hen's egg. It may be firm

or soft, and is sometimes pulsatile, and in many cases the surface is covered by numerous large, tortuous vessels. A definite capsule is usually present, from which septa pass to the inside of the tumour. The cut surface has a spongy, pink or greyish-red appearance, and there is often evidence of hæmorrhage. From their shape, lobulation, and greyish surface such tumours have been called "potato tumours."



FIG. 184. Carotid body tumour. The cells are large and clear and are in solid alveoli.

(Laboratory of Royal College of Physicians of Edinburgh.)

The growth applies itself closely to the carotid vessels, which often become incorporated in the tumour or may even be compressed by it. Owing to its fixation to the vessels the tumour is movable laterally but not vertically.

Microscopically, the tumour shows very variable features, and it has therefore been found difficult to devise a satisfactory pathological designation for it. The common appearance, in the more differentiated parts of the tumour, is that of masses of polyhedral

granular cells arranged in whorls around blood vessels, and nerve twigs are often incorporated within the cell bundles. Chromaffin may be evident in the cells. The blood vessels, in the form of sinusoids, may be very numerous and give the tumour a hæmangiomatous appearance. There is evidence, on histological grounds, that the tumour is akin to the glomus tumour of the skin and the neuroblastomas of the sympathetic nervous system.

The majority of carotid body tumours are innocent and grow very slowly. But in a few instances, after persisting for many years they may suddenly show rapid growth with features of malignancy, so that at operation definite evidence of infiltration of the large blood vessels, the pharynx, and other neighbouring structures may be found. Metastases may arise in the lymph glands, but distant metastases do not occur.

From the surgical point of view it is found that the tumour may be shelled out in a few cases. But in others, on account of adhesion to the carotid artery, jugular vein, and large nerves, it may be necessary to sacrifice parts of these structures. It is for this reason that the operative treatment of carotid body tumours is often a serious undertaking. The mortality rate is about 30%, and this is accounted for by cerebral œdema, following on ligature of the carotid vessels.

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CHAPTER XIX

DISEASES OF THE THYROID GLAND

ANATOMY AND PHYSIOLOGY

THE normal thyroid gland is pale pink in colour, of soft consistency, and smooth or slightly uneven on the surface; it is enclosed in the pretracheal layer of the cervical fascia. The cut surface is greyish-red and glistens slightly from the colloid material it contains.

The gland is divided into lobules by a connective-tissue stroma derived from intrusions of its areolar capsule. Each lobule contains a number of acini or gland follicles. The acini vary in diameter and are spherical or polyhedral and lined with a single layer of low columnar epithelium. The cells have no basement membrane and rest directly on a stratum of areolar tissue, in which lie numerous blood vessels and lymph channels; the finer vessels are of sinusoidal character and lie in contact with the vesicular epithelium. Adjacent to some of the acini there are groups of spheroidal cells whose function is probably to replace effete vesicles. Lymphocytes are present in the interstices of the gland and aggregations of them may be a prominent feature.

The acini are filled with an iodine-containing viscous fluid—*colloid*—which stains a bright pink with eosin. The colloid is regarded as the specific secretion of the thyroid cells, and the amount in the vesicles varies inversely with the activity of the gland. Generally it may be assumed that an excessive accumulation denotes inactivity on the part of the gland (*storage phase*), and diminution signifies activity of the gland (*secretory phase*).

The appearance of the vesicles varies with the state of activity of the thyroid. The resting vesicle is distended with colloid; the cells are cubical; the protoplasm of the cells and of the centrally placed nucleus stains rather faintly and shows few granules. The active vesicle is irregular in shape and is collapsed; colloid is absent or present only in small amount and is more fluid; the cells are larger and tend to be columnar; their nuclei are larger and placed peripherally, and the granules stain more deeply.

The thyroid gland has the special property of abstracting iodine from the blood. Normally the iodine content amounts to 0.01 to 1.15% of the dried weight of the gland—amounts in striking contrast to 0.001%, the maximum for any other tissue. The avidity of the gland for iodine is illustrated by the experiments of Marine and Rogoff, who showed that in dogs intravenous injection of 50 mgm. of potassium iodide increased the iodine content by several hundred per cent. in five minutes.

Iodine is utilized by the thyroid gland in the elaboration of its specific hormone—*thyroxin*. Thyroxin was first isolated from the gland by Kendall in 1915 and was prepared synthetically by Harrington in

1927. Various forms of thyroxin have subsequently been identified, but the exact constitution of the natural secretion is not finally settled; but the most recent investigations suggest that it may be a compound of optically-active thyroxin and a polypeptide, derived ultimately from iodine, tyrosine, and an intermediate product, di-iodotyrosine.

Thyroid extract fed to tadpoles leads to increase in size and rapid metamorphosis, and use is made of this phenomenon in the Gudernatsch test for determination of the quantity of active secretion in thyroid tissue. In human beings administration of thyroid extract gives rise to tachycardia, flushing of the skin and an increased metabolic rate, but the most conspicuous signs of pathological thyrotoxicosis, viz., exophthalmos, tremor and dilatation of the pupil, do not occur. But, recently it has been shown that if thyroid extract is given with drugs such as ephedrine, which stimulates the sympathetic nervous system, exophthalmos develops.

There is a close relationship between the thyroid and the anterior lobe of the pituitary gland. Removal of the anterior lobe of the pituitary is followed by partial atrophy of the thyroid, and, conversely, prolonged administration of pituitary extracts leads to hyperplasia of the thyroid. Thyroidectomy is followed by hypertrophy of the anterior lobe of the pituitary.

It is now known that the anterior lobe of the pituitary contains a specific thyroid-stimulating hormone, which, even *in vitro*, affects its cells. Confirmation of the stimulatory action of the pituitary is evidenced by animal experiment (*e.g.*, in ducks), in which continued injections of extracts produce massive hypertrophy of the thyroid accompanied by exophthalmos.

CLASSIFICATION OF DISEASES OF THE THYROID GLAND

It is barely possible in the present state of our knowledge to formulate a comprehensive classification of thyroid diseases either on an ætiological basis or on the deviations from the normal histology or physiology. But the conceptions of the pathology have been greatly simplified since the importance of iodine deficiency as a causative factor in simple goitre has been recognized and since the essential unity of the toxic forms has been appreciated. Nevertheless, it is usually very difficult to correlate the functional disturbance of thyroid disorders with structural abnormality of the gland.

The various clinical conditions can be considered conveniently under the following headings: (1) congenital abnormalities; (2) acute and chronic thyroiditis, including lymphadenoid goitre (struma lymphomatosa), and ligneous thyroiditis (Riedel's struma); (3) Simple goitre, (a) parenchymatous, (b) diffuse colloid, (c) adenomatous; (4) goitre with thyrotoxicosis (toxic goitre), (a) primary (exophthalmic goitre), (b) secondary (toxic adenoma); (5) tumours.

CONGENITAL ABNORMALITIES

The thyroid gland is developed as early as the third week (1.5 mm. embryo) as a median outgrowth of the entodermal lining of the floor of

the pharynx. The bud as it elongates becomes hollow and its end globular. Evidence of a bilobed structure can be found in a 5-mm. embryo. The connexion of the stalk (now solid) with the pharynx is lost in the 7-mm. embryo, and the separation may occur near the pharynx or more caudally. Separation near the pharynx is believed to favour persistence of a pyramidal lobe or a thyroglossal duct, whereas detachment at a lower level may account for the development of a lingual thyroid rest or a suprahyoid cyst.

Descent of the thyroid gland is probably determined by the caudad movement of the primitive heart and its aortæ and abnormal evolutions of these structures may lead to ectopia of the thyroid or aberrant glands.

A **lingual thyroid** may be associated with absence of the thyroid gland in the neck (about 10%), or it may be a supernumerary gland. It is situated in the median raphe beneath the mucous membrane at the base of the tongue. It is yellowish-red, like a cherry, and is generally sessile, but is occasionally pedunculated. Large and dilated vessels may traverse its surface.

The swelling at the back of the tongue may attract attention in childhood on account of dysphagia or respiratory obstruction, but more often it remains unnoticed until puberty or pregnancy, when, from increased vascularity, hemorrhage, or degeneration, it increases in size. Rarely, malignant change occurs.

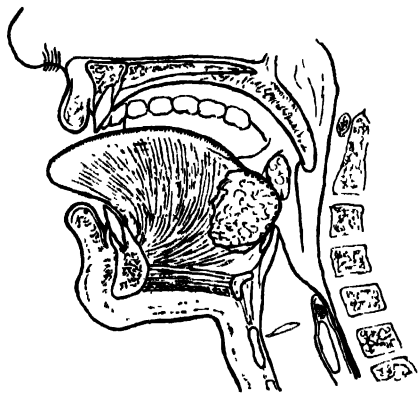


FIG. 185. Diagram of lingual thyroid.
(Department of Surgery, University of Edinburgh.)

triangles of the neck on one or on both sides. They may undergo enlargement either alone or in conjunction with the normally placed thyroid. The origin of such laterally placed portions of thyroid is not understood, but it is conceded that they are specially prone to malignancy, resulting in a papilliferous type of carcinoma. Their dark colour may suggest a melanotic tumour. There is evidence that some such outlying nodules are not of developmental origin, but are the result of metastasis to glands from an inconspicuous papilliferous carcinoma of the thyroid. Supporting evidence is the constancy of the lymphoid capsule the tumours retain and the occasional presence of papilliferous changes within the thyroid gland.

Thyroglossal Cysts and Fistulae. A cyst may occur at any point

Aberrant and Accessory Thyroids. Nodules of thyroid tissue, single or multiple, and of varying size, may occur in the line of the pyramidal process. They may constitute the entire thyroid or be supernumerary glands. Similar nodules may be present in proximity to the inferior extremity of the gland or, in rare instances, in the mediastinum, or even embedded in the trachea.

More commonly outlying and separate nodules of thyroid tissue occur in the anterior or posterior

in the course of the thyroglossal tract, from the foramen cæcum to the isthmus of the thyroid gland, or even as low down as the suprasternal notch. Very occasionally the cysts are multiple. Remnants of the thyroglossal tract are rare above the hyoid, and therefore cysts are correspondingly uncommon in that situation; but, below the hyoid bone, remnants of the tract are often present and cyst formation is consequently fairly common. When the infrahyoid part of the tract is complete it extends in the middle line or slightly to one side of it from the isthmus of the thyroid gland to the hyoid bone, behind which it is usually enfolded.

A thyroglossal cyst may be present at birth, but in the majority of cases it first appears in childhood or in early adult life. The cyst, which varies in size from a pea to a walnut, forms a rounded, tense swelling in the middle line or slightly to one side of the neck. Most commonly the cyst lies immediately below the hyoid bone, but it may be as low as the cricoid cartilage or even the suprasternal notch. Much more rarely the cyst is situated above the hyoid bone and, in that situation, it may bulge into the substance of the tongue or even into the floor of the mouth, as well as beneath the chin. The cyst is thin walled and contains clear, glairy or mucoid fluid; occasionally the contents are dark from cholesterol crystals or altered blood. The cyst is lined with stratified columnar, cubical, or squamous epithelium in varying proportions; in a few the epithelium is purely squamous or columnar and oiliated. Small islets of thyroid tissue may be present in the wall of the cyst. In many cases a considerable amount of lymphoid tissue surrounds the cyst and predisposes it to infection. Frequently a narrow fibrous band extends from the wall of the cyst to the posterior and inferior part of the body of the hyoid bone, and sometimes this prolongation may actually traverse the bone, or it may pass in front of the hyoid and extend to the base of the tongue.

A thyroglossal cyst is very liable to become inflamed, especially after an attack of pharyngitis, and if suppuration occurs the cyst may rupture and form a fistulous opening in the neck—*thyroglossal fistula* or median fistula of the neck. In other instances a fistula results from aspiration or from incomplete removal of the cyst. The fistula is very persistent and discharges glairy fluid or pus continuously or intermittently. Usually a firm cord of tissue can be felt passing from the fistula towards the hyoid bone; and as a result of fibrosis and contracture of the cord, the skin surrounding the orifice is pulled upon and forms a crescentic fold.

Surgically, thyroglossal cysts and fistulæ, on account of their ramifications, require specially planned operations for their eradication. As the prolongation of the cyst or fistula is often attached to the hyoid bone or extends towards the base of the tongue, it is usually necessary to remove a portion of the bone and to excise a tubular portion of the median fibrous raphe of the genio-hyoid muscles.

ACUTE THYROIDITIS

Acute thyroiditis is rare in healthy thyroid glands, but is not uncommon in goitrous ones. It may occur as a complication of typhoid

fever, diphtheria, erysipelas, and a number of cases have followed acute respiratory diseases, especially those associated with influenza. One or both lobes of the gland may be affected. The inflammatory process usually subsides, but suppuration may occur and the resulting abscess may burrow into the œsophagus, the trachea, or the mediastinum.

In rare instances suppuration in the thyroid gland follows perforation of the œsophagus or the trachea by a sharp foreign body. A carcinoma of the pharynx or of the œsophagus may invade the thyroid gland and lead to suppuration.

CHRONIC THYROIDITIS

Tuberculous Thyroiditis. Tuberculosis of the thyroid gland is very rare. It is secondary to tuberculosis elsewhere in the body, and it may affect a healthy gland or an adenomatous one. It may occur in one of three forms : (1) *miliary*, which is similar to miliary tuberculosis of other organs ; (2) *caseous*, an uncommon form, sometimes associated with tuberculous lymphadenitis ; and (3) *sclerosing*, in which one lobe or the entire gland is the seat of extensive fibrosis, and is very hard, elastic, yellowish-white, and fixed to surrounding structures.

Syphilitic Thyroiditis. Syphilis of the thyroid is rare. It may occur in inherited syphilis and it develops usually in early adult life. It may occur also in acquired syphilis.

In syphilitic thyroiditis the gland is moderately enlarged and is diffusely infiltrated by fibrous tissue. It is usually slightly nodular and extremely hard, and as the thyroid often adheres to surrounding structures, resemblance to malignant disease may be very close. In many cases symptoms referable to pressure on the trachea are present and may become urgent.

Microscopically, the gland shows a diffuse infiltration by fibroblasts, giant cells and lymphocytes which replace the tubules. The arteries show endarteritis, and there is regeneration of blood vessels.

Lymphadenoid Goitre : Struma Lymphomatosa (Hashimoto's disease)

This non-specific form of goitre was first described in 1912 by Hashimoto. It possesses characteristic pathological features which class it as a distinct form of thyroid abnormality.

It occurs almost exclusively in women over forty-five years of age, and frequently culminates in myxoœdema, though in rare instances toxic features may appear. The thyroid gland is moderately and uniformly enlarged, smooth and firm, and when cut is pale pink or yellow in colour. Everywhere there is an increase of fibrous tissue leading to exaggeration of the normal lobulation. Colloid containing tissue is absent. Microscopically, the characteristic feature is the uniform and widespread infiltration with lymphocytes, together with many germ follicles, which replace and distort the glandular tissue. In the later stages there may be extensive fibrosis, but it does not extend to the extra-glandular structures.

The pathogenesis of this variety of goitre is obscure. McCarrison reproduced a similar type in rats by feeding them a deficiency diet.

However, in man there is little evidence that deficiencies in dietary are responsible for the disease.

Attempts have been made to establish a relationship between lymphadenoid goitre and ligneous thyroiditis, but it has not been substantiated on either clinical or pathological grounds.

Ligneous Thyroiditis. (Woody Thyroiditis ; Riedel's struma)

This rare form of thyroid affection was first described in 1896 by Riedel, who summed up its main features as "a chronic inflammation of the gland leading to the formation of an iron-hard tumour." From the surgical point of view the disease is of importance because of its simulation of carcinoma.

The most conspicuous feature is a painless enlargement of the thyroid, which is densely hard. The gland is adherent to the trachea and other structures of the neck, and pressure symptoms are generally severe and are out of proportion to the degree of enlargement. Women are more often affected than men, and usually the disease is not associated with either hypothyroidism or hyperthyroidism. The regional lymph glands are not enlarged. Spontaneous retrogression of the disease has been reported, and retrogression has also been known to occur after removal of part of the gland or after exposure to radium.

Pathology. The appearance of the thyroid gland and its relationship to surrounding structures varies according to the duration of the disease. In the early stage it is enlarged irregularly and asymmetrically. Its surface may be smooth or nodular, and the gland is extremely hard, so that a sensation of iron-hardness is imparted when an attempt is made to cut it. The cut surface may show thick grey hyaline bands of fibrous tissue which intersect the gland. The gland is usually adherent to its fascial capsule, and, at a later stage, may be tightly bound to the muscles, trachea, and the carotid sheaths. In the advanced stages, tough, leathery bands of infiltrating connective tissue may extend from the gland, and often they reach the mediastinum or the base of the skull so that it may be difficult to recognize individual structures. The skin usually escapes, but in some instances it is adherent and may be ulcerated.

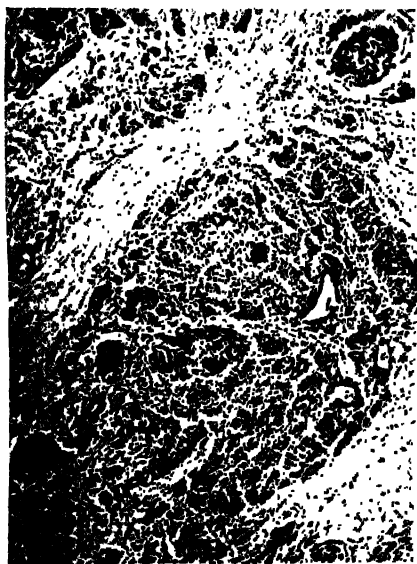


FIG. 186. Ligneous thyroiditis. $\times 55$.
The gland is extensively infiltrated with fibrous tissue containing many lymphocytes.

(Department of Pathology, University of Glasgow.)

The chief histological change is the overgrowth of adult fibrous

tissue often extensively hyalinized. Little of the parenchyma of the gland survives in the zones of fibrosis, but normal tissue is usually

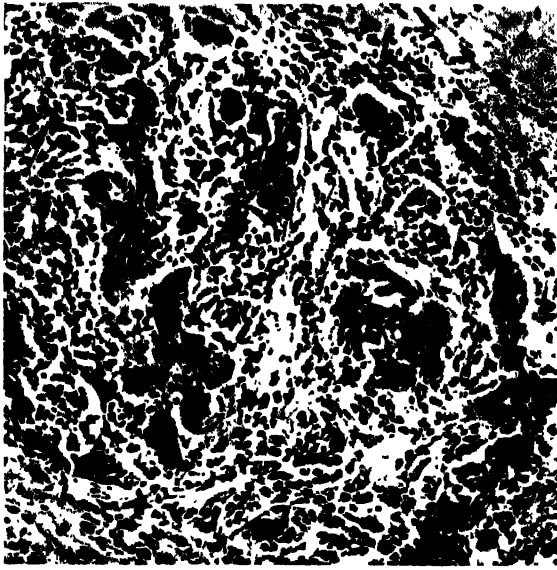


FIG. 187. Ligneous thyroiditis. $\times 150$. Hyperplastic thyroid cells, showing no acinar arrangement, are separated by fibrous tissue containing many lymphocytes.

present at the periphery. Lymphocytic infiltration or aggregations of follicles are lacking.

The cause of these remarkable replacement changes in the thyroid is not known. Neither syphilis nor tuberculosis plays a part. There is no evidence that the condition represents an involuntary stage of a single or lymphomatous goitre.

SIMPLE GOITRE

Ætiology. The importance of iodine deficiency in the production of endemic goitre is fully appreciated. But recent researches have brought to notice other and equally important accessory factors which may favour its occurrence: they are known as *goitrogenic agents*.

Iodine deficiency may be due to lack of iodine in drinking water, in the soil or in foodstuff borne by it. Probably in many instances intake of iodine is adequate, but its utilization is disturbed by alimentary or constitutional abnormalities. However important iodine deprivation may seem in goitre areas, there is not sufficient evidence to prove that it bears an inverse ratio to the incidence of the disease. It is more likely that deficiency of iodine renders the metabolic processes more susceptible to the action of additional goitrogenic agents. In brief, iodine may determine endemicity, superimposed factors (so-called *goitrogenic agents*) its incidence.

Goitrogenic agents include (1) insanitary conditions, (2) faulty diet, (3) chemical substances.

(1) *Insanitary conditions* which permit of contamination of food and drinking water by human and animal excreta have been proved to be fruitful predisposing causes of goitre in localities where the iodine content in the soil is low and the diet faulty. Provision of a purified water supply brings about a notable reduction in the incidence of goitre in such regions.

(2) *Faulty diet* may give rise to goitre in animals under experimental conditions, and presumably may have the same effect in man. The most important agencies are (a) excess of fats, fatty acids and lime, (b) deficiency of iodine, vitamin A, vitamin C, and protein (in association with vitamin A deficiency), (c) the presence in the diet of certain substances, such as cyanogen compounds, found in cabbages. The iodine content of fresh foodstuffs varies greatly in different localities. The minimum requirement of iodine for adults is said to be about 15 mg. per day, but lesser amounts may be adequate provided positive goitrogenic agents are eliminated.

(3) *Chemical substances* have been shown to be goitrogenic in animals. The best known are calcium, boron, silica, organic acids and cyanides. Cyanides apparently act by depressing tissue oxidation, with consequent greater thyroxine requirement and an increased iodine supply to meet its production.

Prophylaxis of Goitre. Striking evidence of the importance of iodine in the prevention of goitre is afforded by statistics from goitre regions following upon the practice of supplying tablets containing iodine to school children. The disease is not eliminated entirely, but its incidence is greatly diminished and is likely to be still more so if all known goitrogenic factors are excluded.



FIG. 188. Photomicrograph of colloid goitre. Note the enlargement of the acini due to excessive accumulation of colloid, and the flattening of their epithelial lining.

(Laboratory of Royal College of Physicians of Edinburgh.)

Varieties of Simple Goitre

Parenchymatous (Chronic Hypertrophic) Goitre. This variety of goitre is uncommon in Great Britain. It is a type more common in mountainous regions such as the Alps and Himalayas, and usually

develops about puberty, although it may be congenital. It is the outcome of continued strain upon the resources of the gland. The thyroid is moderately enlarged, pale in colour, and fleshy like other hyperplastic goitres. Microscopically, the follicles are increased in number, and are small and lined with cubical or low columnar cells; there is little or no colloid, the iodine content is greatly reduced. The appearances of the gland are comparable to those which follow subtotal thyroidectomy in animals. Constitutionally, evidence of slight hypothyroidism is often present.

Simple Colloid Goitre. This condition may occur sporadically or endemically, and is the type met with in lowland regions in Great Britain. It is more common in women than in men and usually begins in early adult life. It is the type of goitre which occurs, usually temporarily, in adolescence or during pregnancy. In endemic areas it is usually succeeded finally by adenomatous changes, usually between thirty to fifty years of age. The disease is characterized by an excessive storage of colloid in the acini, suggesting that a previously hyperplastic gland had involuted beyond the normal limits. The aetiological factors which determine the excessive storage of colloid are not fully understood, but probably excessive intake of calcium and phosphorus relative to iodine is an important underlying cause.

Morbid Anatomy. The thyroid is uniformly and diffusely enlarged and of soft consistency. The cut surface presents a fine honeycomb appearance and is studded with glistening colloid of clear or amber colour. The blood vessels show commensurate enlargement and the fibrous stroma is increased in amount. The iodine content per unit weight is diminished, but the total amount in the gland may exceed normal.

Microscopically, there are areas that look normal, but in most places the acini are widely dilated and are filled with deeply staining colloid, and the lining epithelium is flattened. Areas of active hyperplasia are usually scanty, but may be numerous. The general appearances suggest that the gland has been subjected to the effects of alternating periods of iodine sufficiency and iodine want.

Various secondary changes, such as hæmorrhage and the formation of large colloid cysts, are common; and, after the age of twenty years, adenomatous changes usually develop.

Diffuse colloid goitre may give rise to no other complaint than disfigurement, but in long-standing cases neighbouring structures may be subjected to pressure. Occasionally there are features of slight hypothyroidism.

Adenomatous or Nodular Goitre. This is the commonest variety of goitre. It occurs sporadically or endemically, and its incidence is low in early life but increases with age. In non-goitrous areas about 10% to 15% of thyroid glands examined at autopsy display either macroscopic or microscopic evidence of adenomatous changes.

Formerly the nodular masses characteristic of this type of goitre were regarded as innocent tumours, but they are now believed to represent circumscribed areas of involution developed in a hyperplastic gland. They have their counterpart in chronic lobular mastitis and in some types of cirrhosis of the liver.

The mode of origin of the adenomatous masses is probably as follows: In the process of involution subsequent to hyperplasia the restoration to normal is not necessarily uniform: some parts may remain in a state of hyperplasia, others may involute completely, and others may undergo excessive involution. When the involutionary changes are confined to individual lobules and the rest of the gland remains either temporarily or permanently in a state of hyperplasia the colloid filled vesicles of the involuted portions of gland become demarcated from the rest, and this segregation may become more pronounced by the condensation and overgrowth of fibrous septa which afford an adventitious capsule for the nodules. In a somewhat similar manner persisting areas of hyperplasia may become delineated from the rest of the gland resulting in a more solid type of adenoma. Such a cycle of changes in the thyroid gland may be evolved rapidly or may occupy many years, and as an outcome, the histological appearances may be very complicated. For example, in one gland there may be areas typical of colloid goitre, of adenomatous goitre, and of all grades of hyperplasia.

Morbid Anatomy.

The appearances of the thyroid are extremely varied. Sometimes there is a single adenoma, but more often the tumours are numerous and scattered throughout one or both lobes, and, as a result, the gland may be greatly enlarged. An individual adenoma may be no larger than a pea or it may be as large as an orange. It has usually a well-formed capsule, and if single it can be enucleated. On section it may have a gelatinous or amber appearance, or it may be firm, greyish-yellow and elastic.

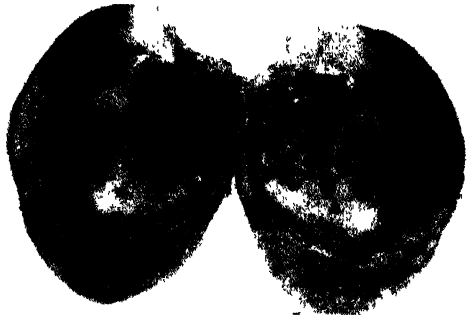


FIG. 189. Adenoma of thyroid gland: the tumour has been bisected.

(Department of Surgery, University of Edinburgh.)

A thyroid adenoma of whatever type is very liable to complications. A solid adenoma may undergo necrosis; a colloid adenoma frequently becomes cystic. The cyst contents are often chocolate coloured from extravasated blood, and cholesterol crystals may be present. Hæmorrhage into an adenoma is a fairly frequent occurrence; it may lead to sudden enlargement of the adenoma and may therefore simulate acute thyroiditis or even malignant disease. Calcification may occur in the capsule or septa of an adenoma or within its partly necrotic contents.

Microscopically, it is customary to distinguish two types of adenoma, the *colloid* and the *fœtal*. The colloid type is composed of large colloid-filled acini, occasionally interspersed with islets of hyperplasia. The capsule is usually well formed and the surrounding

acini are compressed. The remainder of the gland may be normal or it may show diffuse or patchy hyperplasia. In the foetal type, which is

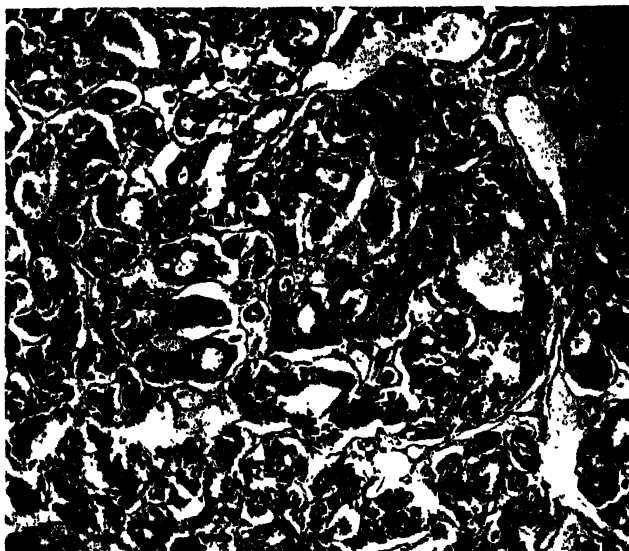


FIG. 190. Adenoma of thyroid gland. $\times 75$.

(Department of Pathology, University of Glasgow.)

usually single, the acinar structure is seldom obvious, the cells are usually cuboidal or spheroidal with large dark staining nuclei and are arranged compactly or in strands or columns. Colloid is seldom present in large quantity.

TOXIC GOITRE

During recent years there has been a tendency to unification in the classification of the various types of toxic goitre, and for descriptive purposes it is convenient to divide cases into two fairly well-defined groups: (1) primary (exophthalmic goitre, primary Graves' disease), and (2) secondary (toxic adenoma).

The term *primary toxic goitre* signifies that toxic features have developed while the thyroid gland is healthy and capable of very prolific activity; whereas the designation *secondary toxic goitre* is applied to those cases in which toxic features develop in connexion with a gland whose activity is altered by disease, either thyroiditis, colloid goitre, or adenomatous goitre. It should be borne in mind that the difference between the two types is one of degree rather than of kind and that all gradations between them may be recognized. In short, toxic goitre (which includes both forms) is a single disease, and its manifestations in different cases are merely modified according to the condition of the thyroid gland when the particular stimuli to activity are imposed upon it, and to a less extent according to the age and the constitution of the patient. In Britain the sex incidence of thyrotoxicosis is about eight females to one male.

Ætiology. Until other evidence is forthcoming the thyroid gland itself must be regarded as the primary source of toxic activity. There is no proof that the excessive secretion it produces is different from the normal. Many attempts have been made to incriminate other endocrine glands in the initiation of the disease and in the final manifestations in various systems of the body. An excessive output of thyrotropic hormone from the pituitary gland has been held responsible but the evidence is not yet complete.

The predisposing causes of toxic goitre are fairly well known. *Primary toxic goitre* occurs most often in young subjects, especially women, and may sometimes develop before puberty. Not infrequently there is history of goitre in the family. Less often the disease develops about the time of the menopause. *Secondary toxic goitre* usually develops in older subjects, usually women after thirty-five years of age or much later.

The exciting causes of toxic goitre are suggested by the frequency with which a history of nervous strain precedes the illness. It may be acute or protracted, and subjects of an emotional or artistic temperament are more susceptible. In other instances infections such as influenza, tonsillitis, etc., precede the illness and may be regarded as exciting factors.

The Thyroid in Toxic Goitre

(a) **Primary Toxic Goitre.** The thyroid gland is enlarged uniformly to a moderate degree.

On an average, it is about four or five times the normal size, but in some cases the enlargement may not be obvious on examination as the gland sometimes insinuates itself behind the trachea. There is no constant relationship between the size of the gland and the severity of the symptoms. The gland is highly vascular, owing to dilatation and proliferation of its blood vessels. The cut surface is granular and friable, and owing to the diminution of colloid it lacks the normal



FIG. 191. Primary toxic goitre associated with hypertrophy of thymus gland.

(Department of Surgery, University of Edinburgh.)

glistening appearance. In old-standing cases there may be a marked increase of the intraglandular stroma. The iodine content of the gland is reduced. In the majority of cases of toxic goitre beginning before the age of thirty years the thymus shows hyperplasia. In some cases

the lymphoid tissue throughout the body shows a mild degree of hyperplasia.

Microscopically, the most characteristic features are reduction in the amount of colloid and proliferation of the epithelial cells lining the acini. The colloid is usually very scanty, and is more fluid than normally and is often vacuolated; it often contains degenerated cells and it stains poorly with eosin. The cells of the acini are enlarged and swollen, increased in number, and definitely columnar. Infolding



FIG. 192. Photomicrograph of thyroid gland from a case of primary toxic goitre. The epithelium of the acini shows marked hyperplasia, the colloid is scanty and vacuolated.

(Laboratory of Royal College of Physicians of Edinburgh.)

of the walls of the acini is usually a striking feature and, as a result, the acini lose their normal shape. An excess of lymphocytes is present in many cases.

The appearance of the thyroid gland in primary toxic goitre varies according to the clinical course of the disease. In cases which run a rapid course without remissions there are only the changes of hypertrophy and hyperplasia as described above, whereas, in cases in which there are natural remissions parts of the gland are hyperplastic and others involuted. In the involuted parts the acini are distended with colloid, and as the involutionary process usually has a lobular distribution these colloid areas frequently become separated from the rest of the gland, forming adenomatous or nodular masses of varying size. The areas of hyperplasia also have a lobular distribution and may become sharply demarcated to form the so-called "miliary adenomata."

Similar involutionary changes follow the therapeutic administration of iodine in primary toxic goitre. They include restoration of colloid to the vesicles, disappearance, in places, of hyperplasia and hypertrophy, and increase of the fibrous stroma and reduction of vascularity. As a result the gland becomes firmer and more gelatinous, and often distinctly mammillated or nodular on the surface. It is well known that iodine produces very marked temporary amelioration of the symptoms in over 70% of cases and rarely fails to effect some benefit.

(b) **Secondary Toxic Goitre (Toxic Adenoma).** In most cases the pre-existing pathological condition is an adenomatous goitre, which may have been present since early adult life. The adenoma, *per se*, does not confer any special tendency to the development of toxicity, but it alters the toxic features very considerably. It appears as if the epithelium in an adenomatous goitre is already, to some extent, exhausted or destroyed, and is unable to react to the same extent as a healthy gland, and therefore the manifestations of secondary toxic goitre are usually less pronounced than those of the primary variety, though the effects upon an already impaired cardiovascular system may be more grave.

It is presumed that excessive secretion is not elaborated in the adenomata but in other parts of the gland, but in a very few cases it must be conceded that a single adenoma, situated in an apparently healthy gland, may be itself responsible for toxic effects, for removal of the adenoma (which is often of small size) rapidly brings about relief from the toxæmia.

Exophthalmos. Exophthalmos is one of the most arresting features of toxic goitre. It is probably due to a combination of causes chief of which are (a) sustained contraction of unstriated muscle fibres within the orbit and eyelids, (b) increase of fat in the socket of the eyeball, and (c) cedematous infiltration of the ocular muscles.

Protrusion of the eyes usually diminishes after surgical treatment of the goitre; but in a few instances (especially in elderly males) it persists or increases, so much so that the eyelids cannot be closed and the cornea is permanently exposed and becomes ulcerated. Continued infection may lead to destruction of the eye (exophthalmic ophthalmoplegia). The persisting exophthalmos is believed, as in experimental conditions, to result from excessive liberation of the pituitary factor responsible for thyrotoxicosis.

TUMOURS OF THE THYROID GLAND

Adenoma

In a previous section it was indicated that the common nodular formations in the thyroid are not true tumours. But there is a small group which have undoubted features of an adenoma. Such a tumour, often called "foetal adenoma" from the primitive character of its cells, is usually single, small, solid, and well encapsuled. Histologically, it is composed of cubical or spheroidal cells containing large dark-staining nuclei and very little faintly staining protoplasm. In the early stages the cells lie in sheets without a lumen or are arranged in columns. In places a lumen may form and a minute amount of colloid appears and the tumour then has the appearance of the thyroid gland in infancy. Development may proceed and large vesicles filled with colloid appear, but the cells lining them remain small and other parts of the tumour retain their undifferentiated character. The remainder of the gland is usually healthy. The tumour is generally functionless, and is prone to early degeneration leading to cyst formation. In rare instances myxœdema has followed removal of a thyroid adenoma, even though the gland appears healthy.

Carcinoma

Carcinoma of the thyroid usually occurs between the ages of fifty and seventy. Unlike other thyroid diseases the incidence is greater in men than women (2·4 : 1).

Carcinoma is specially prone to develop in a gland already altered by disease, particularly the adenomatous type of goitre. For this reason the incidence of malignant disease of the thyroid is high in endemic goitre regions.

Usually malignant disease of the thyroid gland causes neither hyperthyroidism nor hypothyroidism; occasionally, however, the tumour or its metastases elaborate thyrotoxin and thus lead to the changes characteristic of toxic goitre.

The histological appearance in carcinoma of the thyroid gland is very diverse, varying from an epithelial proliferation not dissimilar to that of toxic goitre to a degree of anaplasia which may lead to confusion with sarcoma. It is customary, however, to recognize the following pathological types of growth, although it should be understood that they are not invariably distinct and that many intermediate forms occur. Of these types, the first three are not uncommon, the others rare.

Malignant Adenoma. This tumour occurs especially in endemic goitre regions. It is thought to arise most often in a foetal adenoma. The tumour varies considerably in size and appearance. It may attain large size and exercise its malignant effects mainly by pressure in the neck, or it may give rise to metastases which terminate life whilst the

primary growth remains small. Metastasis may take place to the regional lymph glands or to the skeleton. The sternum, ribs, vertebral column and skull are the bones commonly involved.

The microscopic appearance of the malignant adenoma varies greatly, both in different specimens and in different parts of the same specimen. Most often the appearance is that of cubical or low columnar cells arranged in acini, whilst in places the cells may be disposed in solid masses or present a papillary

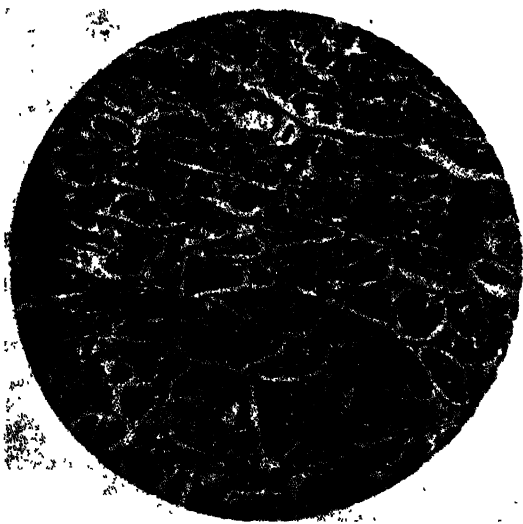


FIG. 193. Malignant adenoma of the thyroid gland.
(Laboratory of Royal College of Physicians of Edinburgh.)

formation. In some tumours there are areas resembling normal or hypoplastic thyroid tissue, or areas with the appearance of foetal adenoma or colloid adenoma.

Papillary Adeno-carcinoma. This tumour, which is the commonest type in Great Britain, is believed to develop generally in an adenoma or simple cyst. Occasionally it has been found in the posterior triangle of the neck, where it is believed to have originated in an aberrant nodule of thyroid tissue. The tumour generally attains considerable size and is soft, partly cystic, with a yellowish-grey cauliflower appearance on section. Since at first it lies within the capsule of the original lesion it is less malignant than the other types. Eventually it gives rise to secondary growths in the regional lymph glands, but it rarely metastasizes to more distant sites.

Microscopically, it is composed of branching papilliferous processes supported by a well formed and vascular stroma; the cells are arranged in one or more layers and may be of a high columnar order, cubical, flattened or syncytial.

Scirrhus Carcinoma. Unlike other types, this tumour commonly arises in a normal thyroid gland. It forms a small hard infiltrating growth which spreads diffusely by direct extension and invades adjacent structures, especially the larynx, trachea and infrahyoid muscles. At an early stage it metastasizes to the lymph glands of the neck and mediastinum.

Microscopically it consists of solid clumps of cells, small, polyhedral or even spindle shaped, set in a fibrous tissue stroma. In some cases the growth is exceedingly cellular and may resemble a sarcoma.

Epidermoid Carcinoma. This tumour resembles the scirrhus carcinoma, but is characterised microscopically by the presence of cells of squamoid pattern. It seems likely that many tumours formerly included in this type were carcinoma originating in the pharynx and involving the thyroid by contact spread.

Sarcoma. It seems probable that many tumours formerly included in this group were anaplastic forms of carcinoma. True sarcoma of the thyroid gland is now regarded as a very rare growth.

Pathological Effects of Carcinoma of the Thyroid. There are no



FIG. 194. Malignant adenoma of the thyroid gland. Solid masses of malignant cells are seen invading an area of normal thyroid tissue.

(Department of Pathology, University of Glasgow.)

characteristic early symptoms and signs of malignant disease of the

thyroid, and this accounts for the frequency with which the disease may not be diagnosed clinically, but is recognized only on histological examination. While a malignant adenoma is still encapsuled diagnosis is scarcely possible.

Progressive or rapid increase in size of a thyroid gland which has already been enlarged but stationary is often an important sign. A very suggestive sign is the sudden onset of hoarseness or aphonia. Pain, referred to the side of the neck or the head, though not pathognomonic is an important symptom. When the tumour has penetrated the capsule of the thyroid, especially if this occurs in the medial aspect of the gland, the larynx and trachea are involved and become fixed, and the trachea may be displaced, compressed or even invaded. The infrahyoid muscles and later the skin become involved in the growth. One or both recurrent laryngeal nerves may be paralysed. Involvement of the pharynx and œsophagus is a not unusual feature and accounts for the dysphagia which is fairly common in this disease. It is very rare for a simple goitre to produce dysphagia, and therefore this symptom, in association with a thyroid enlargement, should arouse a suspicion of malignancy.

In the late stages the skin is puckered and reddened, the superficial veins are engorged, and there is extreme dyspnœa, but cachexia, commonly seen in cancer in other regions of the body, is often absent.

Metastases in Carcinoma of the Thyroid. Next to the regional lymph glands the lungs are the commonest site of metastases. They are also common in the bones, especially in the vertebræ, the skull, and the long bones (*see* p. 179). In a number of cases in which osseous metastases are present the primary growth is very small or of very slow growth, and in such cases the metastasis may be mistaken for a primary tumour.

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CHAPTER XX

DISEASES OF THE PARATHYROID GLANDS

ANATOMY AND PHYSIOLOGY

The parathyroid glands are yellowish-brown ovoid or lenticular structures, measuring 5 to 7 mm. in length and 1 to 2 mm. in thickness. Normally, there are two pairs of parathyroids, superior and inferior, but one parathyroid is absent in 24% of subjects, two are absent in 5%, and occasionally only one is present.

Supernumerary parathyroids are fairly common and as many as twelve may be present. The parathyroids vary in position as well as in number. Usually they lie outside the capsule of the thyroid gland. The superior one is situated on the posterior surface of the lateral lobe, about its middle. The inferior one is larger than the upper and usually lies on the postero-medial aspect of the inferior extremity of the thyroid. The blood supply is usually derived from the anastomotic vessel connecting the superior and inferior thyroid arteries, and this vessel furnishes the best guide to them. In rare instances a parathyroid gland may lie buried within the substance of the thyroid gland. One of the superior parathyroids may lie behind the pharynx or the œsophagus, or in the areolar tissue at the side of the larynx, above the level of the thyroid gland. One of the inferior parathyroids may lie near the bifurcation of the common carotid artery, behind any part of the thyroid gland, on the side of the trachea, or in the superior mediastinum close to the thymus or within it.

The parathyroid glands are composed of compact masses of epithelial cells separated by strands of areolar tissue containing vessels which tend to assume sinusoidal characters. The epithelial cells may vary in appearance according to the age of the subject. Usually they are polygonal and of moderate size with an abundant clear cytoplasm; the cell-nucleus is usually excentric, and contains one to six nucleoli. After the age of ten years slightly larger cells are present, either singly or in groups; they contain granules which are markedly acidophilic. It is not known which type of cell gives rise to the active secretion. Later in life vesicles containing colloid material are sometimes present. The colloid material, which does not contain iodine, is more abundant after thyroidectomy.

The function of the parathyroid glands is to regulate the calcium and phosphorus metabolism of the body. The method by which the glands maintain a balanced ratio between intake, storage, utilization and excretion of calcium is very complicated and is influenced by many accessory factors such as diet, adequate quantities of vitamin D, and a proper amount of phosphatase in the tissues. Upon the correct metabolism of calcium depends the growth and stability of the skeleton, the

irritability of muscles and nerves and the coagulability of blood. The skeleton, being the reservoir for calcium in the body, is especially subject to the hormonal effects of the glands; and in pathological conditions this source of calcium seems to be more readily available for assimilation by the tissues than the calcium absorbed by the bowel.

The amount of calcium in the blood remains very constant and is normally between 9 and 11 mg. per 100 c.cm. of blood serum. The manner in which calcium is held in solution in the blood plasma is twofold. Part, about 2.5 to 4.5 mg., is held by adsorption with protein and is non-ionized and physiologically inactive. The remainder is present as ionized calcium, about 1 to 2 mg. of which is dissolved as it would be in saline solution, and the rest (nearly half) is held in solution by parathormone. The method by which the hormone controls the solution is not fully understood, but when the parathyroid glands are excised it is this last fraction which disappears. There is a reciprocal relation between the concentration of calcium and phosphorus in the blood plasma whereby the acid-base metabolism of the body is maintained, so that if the concentration of one rises that of the other falls.

After removal of the parathyroid glands the blood calcium may fall as low as 6 mg. per 100 c.cm. (*hypocalcæmia*), and the reduction is associated with characteristic clinical features known as *tetany*. The features of tetany are abolished by the administration of calcium salts. Conversely, in certain states of over-activity of the parathyroid glands the blood calcium is raised (*hypercalcæmia*), sometimes to as much as 15 to 28 mg. per 100 c.cm., with a proportionate fall in the blood phosphorus to as low as 1 mg. per 100 c.cm., and a greatly increased output of both calcium and phosphorus in the urine.

The isolation by Collip in 1924 of an active extract of the parathyroid glands afforded new avenues for the study of the parathyroid glands in relation to calcium metabolism. Continued injection in growing animals is followed by a considerable rise in the blood calcium and an increased excretion of calcium and phosphorus in the urine. The plasma phosphatase is always increased. The first effect of parathormone is to lead to an increased elimination of phosphorus by the urine, followed by increase of serum calcium made available by the reserves in the skeleton. The excess of calcium is excreted by the kidney and a progressive depletion of the mineral calcium of the skeleton occurs, resulting in rarefaction of the bones. There may be an associated loss of appetite, drowsiness, muscular atonia, and great dehydration. Metastatic calcification may occur in the kidneys, lungs, myocardium and gastro-intestinal tract. These biological effects of excessive doses of parathormone have their counterpart in generalized osteitis fibrosa (*see p. 150*).

SYNDROMES OF PARATHYROID DISEASE

Hypoparathyroidism

Parathyroid deficiency is manifest in its most characteristic form as post-operative tetany, following operations on the thyroid gland; but it may occur spontaneously.

Post-operative Hypoparathyroidism (*tetania parathyreopriva*). Post-operative tetany is an occasional complication after thyroidectomy for either colloid or toxic goitre. Fortunately, in most cases, the tetany is of a temporary character, and is due probably to temporary suppression of secretion caused by reactionary oedema in the glands. Complete removal of the parathyroid glands is followed by a rapid fall in the serum calcium to 5 or 6 mg. per 100 c.cm., and then tetany usually appears within two to four days of operation. Tetany occurs frequently after removal of a parathyroid tumour; generally it is transient, but it may be complete and prove fatal.

It is supposed that half the parathyroid tissue normally available should be left to prevent tetany. Administration of parathormone restores the serum calcium to the normal level, and has been used successfully to counteract the symptoms of tetany. Calcium chloride injected intravenously has the same effect and acts more rapidly. Parathyroid extract given over long periods may lose its effect, and in such cases vitamin D in the form of 'Calciferol' is effective in controlling symptoms.

The hypocalcæmia of parathyroid origin is associated with retention of calcium and phosphorus in the body and is not due to depletion by urinary excretion. Probably in the absence of parathyroid hormone the tissues are unable to utilize the calcium in circulation, and storage in the skeleton results.

Spontaneous Hypoparathyroidism. The occurrence of spontaneous hypoparathyroidism is well known. It is characterized by weakness, sometimes by opacities in the lens, brittleness and ridging of the nails, and loss of hair and dental enamel. The serum content of calcium is low. The condition is relieved by the administration of parathyroid extract or irradiated ergosterol.

The idiopathic tetany of childhood, which commonly occurs during the active stages of rickets, is associated with a low calcium content of the blood serum. The parathyroid glands often show enlargement in rickets, and probably this is of a compensatory nature to overcome the effects of deficient absorption of phosphorus.

Tetany may result from continued vomiting, *e.g.*, in pyloric or high intestinal obstruction; or it may follow the administration of alkalis, *e.g.*, in the treatment of peptic ulcer or pyelitis. The tetany in such cases is not associated with any alteration of the serum calcium nor related to parathyroid disorder, but is due to alkalosis, which causes a decrease of the available calcium existing as free ions.

Hyperparathyroidism

The association between hyperfunction of a parathyroid tumour and generalized osteitis fibrosa is now fully established, and it is beyond doubt that the parathyroid activity is primary and the skeletal changes secondary.

The parathyroid enlargement is usually confined to one gland, less

often to part of two glands. In rare cases there is overgrowth of all glands, a feature which suggests an indirect hormonal effect probably from the pituitary. The degree of enlargement varies, but, on an average, it is three to eight times the normal before serious symptoms are produced. Usually exploratory operation is required to demonstrate the enlargement. In many instances the enlarged gland has been abnormally situated, *e.g.*, behind the trachea or in the mediastinum.

Continued over-production of parathyroid hormone leads to an obvious alteration in calcium and phosphorus metabolism, which is finally reflected in the dystrophic changes in the skeleton. The serum calcium is raised with individual variations between 12.6 and 23.6 mg. %, and the inorganic blood phosphorus is lowered to a level ranging from 1 to 2.7 mg. %. And, as in all diseases in which decalcification of the skeleton proceeds, the blood phosphatase rises. Calcium excretion by the kidneys is always increased, sometimes tenfold. In addition, there are often additional signs of over-production of parathyroid hormone, comparable to those observed experimentally, in the form of muscular hypotonia, gastro-intestinal disturbances, impaired renal function, abnormal depositions of lime salts, and a liability to calculus formation. In a few cases an abnormally high serum calcium is absent, but there is always an increased excretion of calcium in the urine.

After removal of a parathyroid adenoma the blood calcium and phosphorus promptly return to normal levels. There is usually relief from subjective symptoms, such as bone pains, and spontaneous fractures may heal and osteoclastic tumours disappear. Restitution of the skeletal density is usually progressive, especially in young subjects.

Urinary calculi may break up and disappear or require removal.

Tetany sometimes fatal may develop after operation, even when the blood calcium is as high as 10 mg. per 100 c.cm.

Hypertrophy of all the parathyroid glands has been observed in osteomalacia, renal rickets, and in famine osteodystrophy, etc. Estimation of calcium-phosphorus balance usually serves to exclude a parathyroid origin of the bone dystrophies in such cases.

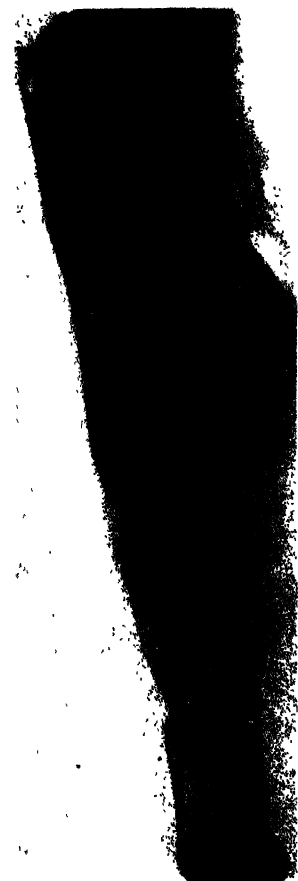


FIG. 105. Radiogram illustrating osteitis fibrosa cystica in the tibia. The rarefaction and cyst formation are very pronounced. Note the fractures in the proximal and the distal part of the diaphysis.

TUMOURS

Tumours of the parathyroid glands are rare, but they are of great interest because they are often, though not always, associated with hyperparathyroidism. There are two varieties—adenoma and carcinoma.

Adenoma. As in many other glandular organs, there is not always a sharp distinction between hyperplasia of the parathyroid gland and adenoma. Usually the adenoma is single, yellow or greyish-white, encapsulated and lobulated. Usually small, examples with dimensions of $7.5 \times 5 \times 1.8$ cm. have been encountered. Even such large growths

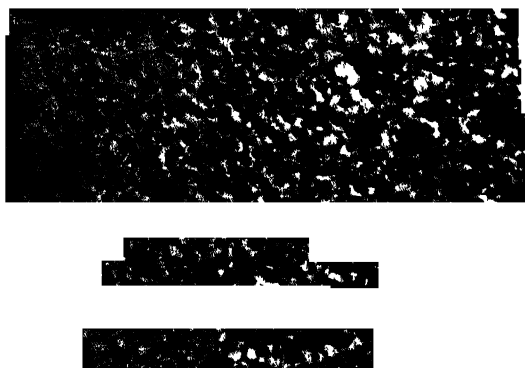


FIG. 196. Adenoma of parathyroid gland. There are solid masses of large clear cells with dark staining nuclei. In addition, acini are seen lined by clear columnar cells.

(Laboratory of Royal College of Physicians of Edinburgh.)

may be palpable. The tumour may be cystic and there may be areas of calcification in it.

Microscopically, a parathyroid adenoma is composed of interlacing compact cords or masses of large clear cells, uniform in type and separated by vascular spaces (*see* Fig. 196). The stroma is usually scanty. In some examples the cells may in parts be arranged in acini containing colloid-like material.

Carcinoma. This is a very rare tumour of the parathyroids. It may arise spontaneously or from an adenoma. The tumour, which grows rapidly and irregularly, may reach the size of a fist or larger. It infiltrates the thyroid gland, the muscles, and the trachea and larynx, and there is a great tendency to local recurrence after operation. Metastases occur in the lymph glands, the lungs, and the skeleton.

Histologically the tumour is composed of irregularly disposed atypical cells of various sizes. The cell nucleus is often large and commonly shows mitosis.

Carcinoma of the parathyroid glands is practically never associated with skeletal disease.

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CHAPTER XXI

DISEASES OF THE PHARYNX, LARYNX AND ŒSOPHAGUS

PHARYNGEAL DIVERTICULUM

A DIVERTICULUM of the pharynx originates as a protrusion of the mucous membrane through the posterior wall of the pharynx in the middle line. The site of origin of the pouch is constant, and is determined by the arrangement of the muscle fibres at the entrance to the œsophagus. The inferior constrictor muscle of the pharynx consists of two portions, each with a different disposition of muscle fibres, and a different action. The upper fibres (thyro-pharyngeus) take origin from the thyroid cartilage on each side and pass obliquely upwards and backwards around the pharynx to its median raphe. The lower fibres (cricopharyngeus) arise from the cricoid cartilage and encircle the entrance to the œsophagus like a collar. Posteriorly, between the two parts of the inferior constrictor, the wall of the pharynx is potentially weak and, under abnormal conditions, constitutes an area of lessened resistance. On the pharyngeal surface this area may be marked by a small depression which has been called the "pharyngeal dimple," although it is rarely detectable in normal subjects. When a diverticulum of the pharynx occurs it is between the two sets of fibres of the inferior constrictor muscle.

Ætiology. There is no evidence that a diverticulum at this site is congenital in origin, for its occurrence in young subjects is unknown apart from organic stenosis of the upper part of the œsophagus. Most examples of pharyngeal diverticulum have been found in adults past middle life, and the incidence is greater in males than in females (3 : 1).

The determining cause of the formation of the diverticulum is accepted to be interference with the normal coordination of the act of swallowing, whereby intrapharyngeal tension, generated during deglutition, is unduly prolonged. The importance of this factor is suggested by the long history of dysphagia even though there may be long intermissions. The mechanism of swallowing can be observed on pharyngoscopic examination or in cases of suicidal cut-throat, and it is then seen that the upper orifice of the œsophagus relaxes only for a brief interval after contraction of the detrusor muscles above it, and that when saliva or a bolus of food has been transmitted it closes at once. Keith measured the pressure generated in the pharynx on deglutition and found it rose to a maximum of 45 mm. of mercury ; such intermittent pressure, if unduly sustained, would doubtless produce strain at the point of obstruction. In the production of a diverticulum it is believed that there is some degree of neuromuscular incoordination in the act of swallowing by which the cricopharyngeus muscle fails to relax in

the normal way in succession to the contraction of the pharyngeal muscles above it (achalasia); and that by repetition of intermittent impulses of high pressure, the least supported area of the pharynx, (especially if already weakened in age), gradually stretches. Once formed, the hernial protrusion increases in size progressively by the weight of its contents; the displacement forwards of the upper aperture of the œsophagus renders more difficult the passage of food into the œsophagus, and the propulsive force of the pharynx is expended in



FIG. 197. Pharyngeal diverticulum.

dilating the sac. It is for this reason that no food enters the œsophagus until the diverticulum is filled. A pharyngeal diverticulum has been observed in association with goitre, and the pressure exerted by the enlarged thyroid, either on the œsophagus or the recurrent laryngeal nerves, has been held responsible. A median diverticulum, arising at the lower end of the pharynx and protruding between the œsophagus and trachea, has been described.

Anatomical Relations and Structure of the Diverticulum. A pharyngeal diverticulum when small retains a partial covering of muscle fibres acquired from the inferior constrictor. With increase in size of the pouch the muscular coat becomes gradually attenuated,

until finally muscle fibres are present only at its neck. The pouch is usually flask-shaped; in a very few instances the fundus of the sac is bifid. The pouch descends behind the œsophagus, situated in the space between the pretracheal and prevertebral fasciæ, and, when large, the fundus may reach the superior mediastinum (*see* Fig. 197). In some cases the diverticulum presses upon and leads to atrophy of the posterior wall of the œsophagus. The diverticulum is usually inclined to one or other side, generally the left, and after a meal a swelling, which gurgles, may be obvious in the posterior triangle of the neck. The dragging effect of the diverticulum brings its mouth into the same axis as the pharynx, and the entrance of the œsophagus appears as a narrow aperture at the anterior border of the neck of the sac. The orifice of the diverticulum is circular or elliptical. Radiographic examination after an opaque meal reveals the size of the pouch and demonstrates how it must fill before food can enter the gullet.

The wall of the pouch varies in thickness in different specimens. It is lined with squamous epithelium which may be smooth or rugose, and which may undergo ulceration or hyperkeratosis. A muscularis mucosæ may or may not be present. The outer fibrous coat, which makes up most of the thickness of the wall of the pouch, is derived from the pharyngeal aponeurosis. This coat is separated from the submucosa by thin areolar tissue, which may afford a plane of cleavage in operating.

Stagnation of food and saliva may lead to ulceration of the interior of the diverticulum and may cause perforation with abscess formation in the neck or mediastinum. Emaciation often ensues from the prolonged difficulty in swallowing. Aspiration pneumonia from regurgitation of the stagnant contents of the sac is not an infrequent cause of death. Occasionally a carcinoma has taken origin inside a diverticulum, even after operation.

Lateral Pharyngeal Diverticulum

This variety of diverticulum is of developmental origin. It is thin walled and deeply situated, and has usually a communication with the tonsillar or the pyriform fossa and sometimes with the skin surface. It is lined by squamous epithelium. Distension within its cavity may lead to severe pressure effects.

LARYNGOCELE (Cervical Aerocele)

This is an air-containing sac which results from herniation of the mucous membrane of the larynx through a defect in the laryngeal skeleton. A similar condition is normally found in a high state of development in some of the higher apes.

Laryngocele may arise in children, but more often it occurs in adults as a result of chronic expiratory obstruction. It is seen in glass-blowers, players of wind instruments, and sufferers from chronic cough. Two types are recognized—internal and external laryngocele.

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Internal laryngocele results from dilatation of the "saccus laryngis" at the anterior end of the ventricle of the larynx. It presents a tense cystic swelling above one vocal cord, and may cause dysphonia or dyspnoea or even dysphagia.

External laryngocele is due to protrusion of the mucous membrane through the thyro-hyoid membrane. It gives rise to a painless swelling in the neck, which enlarges on forced respiration and empties with a gurgle either spontaneously or on pressure. The cyst tends to increase in size gradually and may reach as far as the clavicle. It may be bilateral.

CARCINOMA OF THE PHARYNX AND LARYNX

In the pharynx there are two common starting points for cancer—(1) at the upper aperture of the larynx (epilaryngeal growths), and (2) at the narrow or tubular part of the pharynx behind the cricoid (hypopharyngeal growths). The growths are of the nature of squamous-cell carcinoma, in which cell-nest formation usually is present. Occasionally a basal-cell type of growth occurs; and sometimes the tumour has an abundant lymphoid stroma (lympho-epithelioma).

Epilaryngeal Growths. Epilaryngeal growths are commoner in men than in women and occur most often after the age of fifty years. The growth generally takes the form of a raised ulcer; sometimes papillary types occur, but less often than at other sites in the pharynx. There are four common starting points for the growth: (1) The epiglottis. (2) The ary-epiglottic fold, *i.e.*, in the medial wall of the piriform recess. (3) The floor of the piriform recess, and (4) The lateral wall of the piriform recess. Growths of the epiglottis tend to spread to the valleculæ and to invade the base of the tongue. The epiglottis may be entirely destroyed. Growths of the ary-epiglottic fold may extend into the interior of the larynx and towards the lateral wall of the pharynx. Growths on the floor of the piriform recess are situated most unfavourably, because symptoms are long delayed, and spread to the larynx is of common occurrence. In some instances the tumour in the piriform recess remains very small and a large glandular metastasis appears below the angle of the mandible. The swelling in the neck may be explored and its primary origin entirely overlooked.

The effects produced by epilaryngeal growths are generally different from those at other sites in the pharynx. Tickling in the pharynx, the sensation that a foreign body is lodged there, and discomfort in swallowing saliva apart from food are usually the earliest evidence, and pain and hoarseness are of later occurrence. On laryngoscopic examination the growth can usually be seen and it is often covered by rather tenacious exudate, which may be blood-stained. It is characteristic that the exudate is not readily dislodged in making swallowing movements. The cartilages at the upper aperture of the larynx tend to become fixed, and the surrounding mucous membrane is often cedematous and congested. Involvement of the cervical lymph glands cannot on the whole be regarded as either an early or a conspicuous feature of epilaryngeal growths with the exception of growths of the piriform recess.

Hypopharyngeal Growths. (Post-cricoid cancer.) Hypopharyngeal growths are especially common in women, and quite frequently they occur before forty years of age. As emphasized by Logan Turner, many subjects who develop cancer at this site have for years suffered from intermittent difficulty in swallowing of nervous origin.

The common starting points are the lateral or posterior walls of the lowest part of the pharynx. The growth generally takes the form of a



FIG. 199. Radiogram of thorax in a case of post-cricoid cancer in a man aged seventy-one years. The trachea and bronchi contain barium as a result of regurgitation of an opaque meal into the larynx. Death due to septic bronchopneumonia.

slightly raised papillary excrescence of roughly circular outline. It tends to encircle the pharynx and to extend to the laryngeal cartilages, especially upwards to the arytenoids. At a later stage extension to the thyroid gland is common. The lymph glands in one or both posterior triangles may be invaded. A growth situated at the junction of the pharynx and œsophagus may extend for a considerable distance down the gullet. When that happens it may perforate the trachea and produce a fistula.

Growths in the lowest part of the pharynx are too distant to be seen by laryngoscopic examination, but suggestive signs are œdema and

fixation of one of the arytenoid cartilages and stagnation of exudate. In the advanced stages it may be impossible to state from what point the growth originated. It may displace the larynx forwards, or may be palpable in the neck. From perforation, an abscess may form in the neck or in the mediastinum. A common cause of death is septic pneumonia as a result of regurgitation of food into the larynx owing to obstruction at the entrance of the œsophagus (Fig. 198).

Intrinsic Carcinoma of the Larynx. Intrinsic carcinoma of the larynx usually begins in one of the vocal folds; much less often in one of the ventricular folds, and very rarely in the subglottic region. The favourite site of origin is the anterior half of the vocal fold at its free border, from which the tumour tends to spread forwards and to the opposite vocal cord. The growth is usually of a warty or cauliflower type and has the histological characters of a squamous-cell carcinoma.

It is characteristic of intrinsic cancer of the larynx that it grows slowly, and many years may elapse before the larynx is extensively invaded. Metastases occur in the glands around the carotid sheath. Recurrence of disease in these glands is common after operation.

Intrinsic cancer of the larynx is rare before the age of fifty years, and is more than ten times commoner in men than in women. The chief effect of the growth is to lead to changes in the voice, but at a later stage it may give rise to aphonia, dyspnoea and stridor, and eventually leads to death from hæmorrhage, asphyxia or septic pneumonia.

SPASM AT THE ENTRANCE OF THE ŒSOPHAGUS

This is a common cause of dysphagia. Its underlying cause is spasm of the cricopharyngeus part of the inferior constrictor muscle. It occurs most often in neurotic subjects, especially middle-aged anæmic women, and is generally of long duration before it comes under observation. In rare cases the muscle is greatly hypertrophied.

The appearances noted at the lower part of the pharynx are fairly constant and characteristic. The mucous membrane, instead of being disposed in stellate folds that separate readily, presents a drawn and irregular appearance. The œsophageal orifice is small, often excentric, and may be slit-like; it is readily fissured and, therefore, if a bougie is passed it must be done carefully. Brown Kelly noted that anæsthesia did not bring about relaxation of the spasmodic contraction, but that dilatation effected relief.

In subjects of this disorder the mucous membrane of the mouth and pharynx generally undergo changes. The tongue is abnormally smooth from atrophy of its filiform papillæ and may show fissures or leukoplakia. The cheeks and palate are dry and have a waxy pallor. Saliva is usually scanty but may be excessive.

Anæmia and occasional splenic enlargement may be associated with this condition and recent observations suggest that relief may be gained by full doses of iron and an adequate diet.

Nervous difficulty in swallowing, especially in women, has preceded cancer of the pharynx in a large proportion of cases. Possibly the

growth arises as a result of chronic irritation caused by the functional incoordination or the nutritional deficiency.

CONGENITAL ABNORMALITIES OF THE ŒSOPHAGUS

At about the third week of development of the embryo the Œsophagus is represented merely by an annular constriction between the pharynx and the stomach, and it is only after elongation of the neck and the growth of the lung buds that it becomes tubular. In the early stages of development the cephalad part of the Œsophagus and the trachea form a single short canal, and later the two tubes become separated by

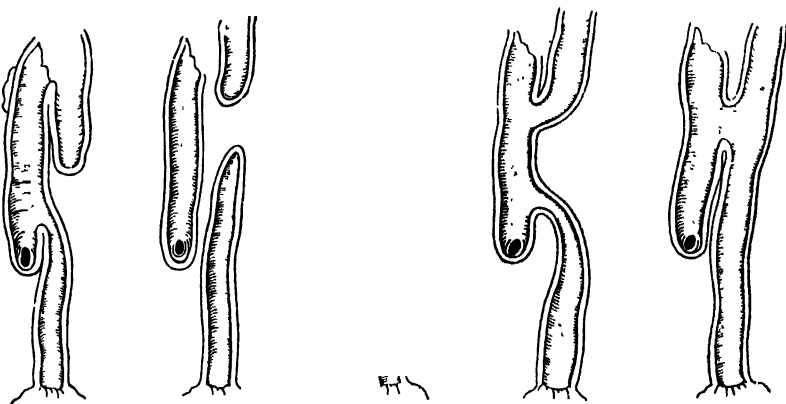


FIG. 199. Diagrammatic representation of congenital abnormalities of the Œsophagus and trachea. The third figure depicts an occluding diaphragm of mucous membrane. (After Vincent.)

the ingrowth of a longitudinal septum from each side, which completes the partition. The caudal part of the septum is the last to be completed.

As the Œsophagus and trachea have a common origin it is not surprising that sometimes fistulous channels persist. Such congenital maldevelopments are generally incompatible with life. The communication is commonest with the trachea at its bifurcation or with the right bronchus. In some instances the Œsophagus and trachea communicate at two points and a segment of the Œsophagus is absent. The other abnormal connexions of the Œsophagus and trachea are depicted diagrammatically in Fig. 199.

Congenital maldevelopment of the Œsophagus itself is of more importance than tracheo-Œsophageal fistulæ because it is often compatible with life, and may be a cause of dysphagia in childhood. The chief types are : (1) congenital narrowing of the whole Œsophagus, (2) congenital stenosis of the upper or the lower end, (3) absence or narrowing of a segment, (4) an occluding diaphragm of mucous membrane, and (5) congenital shortening.

Congenital narrowing of the Œsophagus may be so extreme that the

organ is represented merely by a fibrous cord, but in many instances the œsophagus is properly developed, but in miniature. The recognition of congenital constriction of the œsophagus in infancy depends on the degree of obstruction. If the stenosis be complete all food is regurgitated, but in many cases narrowing causes no symptoms as long as the diet is fluid. In a few cases a congenital web of mucous membrane has been recognized by œsophagoscopy and has been successfully perforated.

In *congenital shortening* the œsophagus ends about the level of the eighth thoracic vertebra. A portion of the stomach is therefore held suspended in the posterior mediastinum above the hiatus in the diaphragm (thoracic stomach). The importance of this developmental abnormality is its simulation of parœsophageal hernia as well as certain types of cardiospasm and dyspepsia.

Ulceration of an intractable kind is particularly liable to occur at the junction of the œsophagus and the stomach.

Œsophageal Diverticulum

Diverticula of the œsophagus are rare and unimportant, as they are seldom discovered during life and rarely give rise to symptoms.

It is customary to describe three varieties : (1) congenital or developmental, (2) traction, and (3) pulsion, diverticulum.

(1) A small diverticulum may result from imperfect separation of the trachea and œsophagus. It occurs usually in the anterior wall of the œsophagus about the angle of bifurcation of the trachea, and is firmly incorporated with the membranous wall of the trachea. The pouch is covered at its neck and sides by muscle bundles derived from the œsophagus.

At or about the level of the bifurcation of the trachea developmental defects in the œsophageal musculature are common and through these small diverticula may emerge. The muscular defects probably represent incomplete coalescence of the relatively thin striated muscle fibres of the upper part of the œsophagus with the stouter plain muscle of the lower part.

(2) A traction diverticulum is usually situated in the neighbourhood of the bifurcation of the trachea or where the left bronchus crosses the œsophagus, and usually owes its origin to adhesion of enlarged tuberculous tracheo-bronchial glands to the wall of the œsophagus. Less often adhesion of the pleura or the pericardium to the œsophagus may determine its development. The movements of respiration and deglutition exert a gradual dragging on the walls of the œsophagus so that finally they may be drawn out into the form of a funnel or diverticulum. Such a diverticulum is usually wide mouthed and of small size, and more than one may be present. As a traction diverticulum is wide mouthed, and as the fundus is often situated at a higher level than its entrance, food does not tend to stagnate. Perforation by a foreign body lodged within its cavity has been recorded.

(3) Pulsion diverticula are very rare. A variety known as *epiphrenic* sometimes occurs in the lower part of the œsophagus on the

left side. It consists of a protrusion of the mucous membrane through the longitudinal muscle fibres of the œsophagus. The communication with the œsophagus may be very minute so that the pouch may become greatly distended with mucoid fluid.

Occasionally pouching and diverticulum formation occur immediately above an old-standing fibrous stricture.

CARDIOSPASM: ACHALASIA OF THE ŒSOPHAGUS

This condition is characterized by dilatation and hypertrophy of the œsophagus associated with a peculiar type of obstruction at its lower end. It affects women slightly more often than men, and it begins insidiously and progresses slowly or intermittently during many years. It is rare in childhood; it generally occurs between the ages of twenty-five and forty-five years, but it may not be present till old age. Symptoms sometimes appear for the first time after a debilitating illness.

The obstruction at the lower end of the œsophagus is usually associated with no obvious organic lesion, and appears to be due to functional constriction. It gives rise to difficulty in swallowing, at first slight and intermittent, later severe and constant. The obstructed œsophagus dilates, and foodstuffs and fluid, denied egress at the cardia, stagnate and ferment or else are regurgitated. In the later stages the constant obstruction leads to starvation and emaciation.

Pathological Features. In an advanced case the œsophagus is lengthened by 3 cm. or more, it is greatly dilated and attains a circumference of even 15 cm. Usually the dilatation is most obvious in the lower two-thirds. Inferiorly, the dilatation usually reaches only to the diaphragm; in some cases it extends as far as the stomach—*i.e.*, about 4 cm. lower. Superiorly, in long-standing cases it may extend as far as the cervical portion or even to involve the pharynx. The dilatation varies in shape—elongated,



FIG. 200. Œsophagectasia. Note the extreme dilatation of the œsophagus and the hypertrophy of the circular muscle. The dilatation stops abruptly at the hiatus in the diaphragm.

(Museum of Royal College of Surgeons of Edinburgh.)

fusiform or flask-shaped—or, if greatly lengthened, it may assume a sigmoid outline.

In addition, the œsophagus shows considerable muscular hypertrophy, the muscular coat being increased in thickness from the normal of about 1.5 mm. to as much as 4 mm. or even 7 mm. The hypertrophy, unlike that in simple stricture in which both sets of fibres are affected equally, is due usually to overgrowth of the circular muscle, but in exceptional cases only the longitudinal fibres are affected.



FIG 201. Œsophagectasia in a young subject. The obstruction is situated at the cardia. Note the active peristalsis.

The mucous membrane, stretched and thinned, may undergo various secondary changes, such as inflammation and ulceration, and, as a result of chronic inflammatory changes, may later become thickened and form multiple polypoidal overgrowths.

Particular interest attaches to the pathological changes in the lower end of the œsophagus, and in regard to these there are many conflicting observations. Most observers are agreed that there is, during life, undue narrowing of the œsophagus at the diaphragm, and that usually there is no organic lesion to which the narrowing may be attributed. The muscle of the œsophageal wall, except in rare cases, is not hypertrophied at the point of narrowing compared with above,

nor is there usually any fibrous stricture, and, indeed, in contrast to the dilatation and hypertrophy higher up, the lower end of the œsophagus is almost normal in appearance. In advanced cases there is sometimes considerable diffuse fibrosis which may lead to organic stenosis at the lower end of the œsophagus. Examination during life by means of bougies or the œsophagoscope has yielded contradictory evidence, for whereas some observers have found the lower end of the œsophagus constricted and spastic, others maintain that it is opened and closed on respiration just as in the normal subject. When palpated by the finger

during gastrotomy the lower end of the œsophagus feels somewhat tight and it yields only gradually to dilatation. Radiographic examination after the administration of opaque fluid shows that the lower end of the œsophagus terminates in a funnel-shaped or tapering extremity which passes rather abruptly to the left towards the cardia. Sometimes from the weight of the contained fluid the lower part of the œsophagus sinks below the level of the œsophageal opening in the diaphragm, and then the conical outlet appears to lead from the side of the œsophagus a short distance from its lowest point. A residue of the opaque medium may be observed several hours after its ingestion. Intermittent vigorous contractions of the œsophagus are obvious on fluoroscopic examination.

The Cause of the Disease. Since Hamman, in 1833, first described its principal features, there have been many views as to its causation, and only recently has its ætiology been made more clear. Formerly its origin was attributed to such factors as congenital malformation, phrenospasm and spasmodic contraction of the cardiac sphincter (cardiospasm).

The view now held is that the dilatation and hypertrophy develop gradually and are for a time a result mainly of functional obstruction due to achalasia or lack of relaxation of the lower end of the œsophagus. The œsophagus, like the remainder of the alimentary tract, is supplied by sympathetic and parasympathetic fibres. The sympathetic fibres reach the lower end of the œsophagus *viâ* the thoracic sympathetic chain, the splanchnic nerves, and the cœliac plexus (alongside the left gastric artery); the parasympathetic fibres are from the vagi. Knight's experiments showed that parasympathetic denervation in cats produced a condition analogous to cardiospasm; and that it could be relieved by severance of the sympathetic nervous contributions. Only partial success followed sympathetic denervations in cardiospasm in man, probably on account of interruption of only a few of the nervous pathways.

ULCERS IN THE ŒSOPHAGUS

Ulceration of the mucous membrane of the œsophagus may result from the abrasion by a foreign body, careless instrumentation or burning by corrosive fluids. Following wasting diseases, so-called decubitus ulcers have been found at post-mortem at the upper end of the œsophagus. Ulcers of tuberculous origin are exceedingly rare.

Most interest is attached to peptic ulceration of the œsophagus, which is relatively common, either in association with peptic ulcer of the stomach and duodenum or independently. The ulcer may be of the acute or chronic variety, and is always situated at the distal end of the œsophagus. It has been ascribed to heterotopic islets of fundal-type mucosa, which are found occasionally in the œsophagus.

An acute ulcer is small, superficial, and usually multiple; it may be responsible for hæmatemesis.

A chronic ulcer is usually single, and has the same anatomical characteristics as a similar ulcer in the stomach. It may give rise to severe and fatal hæmatemesis, but perforation into the mediastinum,

pericardium or peritoneum is a more common cause of death. A fibrous stricture may follow healing of the ulcer. From the practical aspect, gastrostomy may be rendered necessary to promote healing of the ulcer or to facilitate treatment of cicatricial stenosis.

TUMOURS OF THE ŒSOPHAGUS

Simple tumours in the œsophagus are rarities. Those reported are submucous lipoma, fibroma and leiomyoma. They may be sessile or pedunculated, and may assume considerable length. The larger ones may cause obstruction of the œsophagus.

Cancer of the Œsophagus

Carcinoma is much the most frequent cause of obstruction of the œsophagus. Cancer at this site—in contrast with other parts of the alimentary canal—has, despite enormous endeavour, given relatively scant reward to surgical efforts. The failure is not due to any peculiar quality of the growths (except that they are often advanced when first recognized), and the patient's strength and resistance are depleted at an early stage, so he is ill-fitted constitutionally to bear the burden of a severe intrathoracic operation.

Like cancer of the mouth, cancer of the œsophagus may owe its origin in some measure to chronic irritation. Except in the cervical portion, where the sex ratio is about equal, the disease is much more common in men than women (5 : 1); therefore, tobacco juice, alcohol, excessively hot food, etc., have been held responsible for irritating the mucous membrane. The disease is commonest after the age of fifty. Leukoplakia of the œsophagus is commonly observed in old subjects, and its presence is often noted in the neighbourhood of a carcinoma, and, as in the tongue, it has been regarded as a precancerous condition. It cannot be claimed that syphilis has any relationship either through its systemic effects or by producing any local predisposition.

Statistics vary as to the frequency with which different parts of the œsophagus may be affected. Growths tend to appear with greatest frequency at those parts of the œsophagus that are subjected to narrowing by the arch of the aorta, the left bronchus, and the diaphragm. Without doubt the most common site is at the level of the arch of the aorta or just below it. Next in frequency is the lower part of the œsophagus, a few centimetres above the diaphragm, and that part may also be involved by carcinoma extending from the cardiac end of the stomach. Primary cancer in the cervical part is rare, but there may be extension from the pharynx. Dual growths have been met with in the œsophagus as in other parts of the alimentary canal. There is no evidence that the malignancy of carcinoma of the œsophagus varies at different levels.

Types of Growth. Cancer of the œsophagus presents itself in two common forms: (a) a flat ulcerating type of growth; (b) a polypoidal or cauliflower type. Intermediate types are quite common. In rare cases an infiltrating scirrhus type that extends over a wide area of the gullet may occur.

The majority of malignant growths of the œsophagus show the

histological features of a squamous-cell carcinoma, but keratinization and cell-nest formation are usually lacking. Sometimes a glandular type of carcinoma is found, and it is believed to originate in the mucous glands, although it has been suggested that heterotopic gastric mucosa or embryonic epithelium in the wall of the œsophagus may explain its occurrence. Basal-cell carcinoma of undifferentiated type is met with in a considerable number of cases, but, unlike the common basal-cell carcinoma of the skin, it is always malignant.

Morbid Anatomy. At first the disease is confined to the mucous membrane and involves a limited area, but by extension it gradually encircles the gullet. It is stated that the lumen may be reduced to 5 mm. before dysphagia occurs. Longitudinal spread is slight in the scirrhus type, though in the cauliflower type it may be considerable. The ulcerating type causes local thickening of the œsophageal wall, and has nodular, raised and everted edges of irregular outline. The older ulcerated portion is hollowed out and the wall of the œsophagus may be much reduced in thickness at this site, and thus lead to perforation. Polypoidal growths have a lobulated or villous appearance, with a friable surface that ulcerates and bleeds readily, and when inspected is generally coated with a blood-stained fœtid discharge. Such a tumour produces obstruction by its bulk rather than by any changes effected in the wall of the œsophagus.

The œsophageal wall above a growth is redder than usual from increased vascularity and appears relatively immobile and stiffened. Patches of leukoplakia are commonly noted in the neighbourhood of the tumour. Hypertrophy of the muscle and dilatation of the lumen are rarely more than slight.

Mode of Spread. Carcinoma of the œsophagus shows considerable variation in its rate of growth and dissemination. In some cases the tumour may grow slowly during a period of a year or more without extending externally and without involvement of the lymph glands; whereas in others it may involve a considerable part of the œsophagus and rapidly invade surrounding structures, or give rise to secondary deposits in lymph glands or even distant parts. Spread of



FIG. 202. Carcinoma of the distal part of the œsophagus.

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University of Edinburgh.)

the disease is mostly by direct extension and infiltration; when the muscular coat is penetrated local pericæso-phagitis occurs and fixes the œsophagus to the mediastinal structures, which may later become involved in the growth. Lymph vascular spread is fairly common and is present in at least 50% of cases at autopsy. A growth in the cervical part of the œsophagus may cause enlargement of the cervical lymph



FIG. 203. Radiogram of an early carcinoma of the œsophagus. The tumour was situated immediately below the arch of the aorta.

glands on one or both sides of the neck. In the thorax the mediastinal lymph glands may be involved; and the glands at the cardia may be involved even though the tumour is in the midzone of the œsophagus. In growths at the lowest part of the œsophagus the celiac lymph glands have been found enlarged and there may be metastases in the liver. Distant spread by the blood stream is unusual; its occurrence has been noted as a result of invasion of the thoracic duct or of the pulmonary veins.

Complications.

Many secondary complications may ensue when an œsophageal cancer spreads outwards or invades adjacent viscera. Acute perforation may occur, resulting in mediastinitis, and widespread

subcutaneous emphysema. Perforation is sometimes gradual and an abscess develops. Invasion of the trachea or a bronchus is of relatively frequent occurrence and leads to aspiration pneumonia. Penetration of the lung with resulting abscess or gangrene is a common terminal feature, but invasion of the pleural cavity with resulting empyema is much less common. In the neck and the upper part of the thorax one or other of the recurrent laryngeal nerves may be involved in the growth. The left recurrent nerve is of greater length than the right and consequently is more frequently implicated. Secondary involvement of the thyroid gland may result from a growth in the cervical part of the œsophagus, and such an extension may be mistaken for a primary tumour of the thyroid gland.

When obstruction occurs, emaciation, sometimes with much toxæmia, is usually rapid, and it is not checked unless early relief is afforded by gastrostomy or other means. When the stomach is exposed at operation it is usually found to be smaller than normal from prolonged reduction in its activity.

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CHAPTER XXII

DISEASES OF THE STOMACH AND DUODENUM

PHYSIOLOGY OF GASTRIC SECRETION AND MOTILITY

THE stomach has several functions. It acts as a mixing chamber for food, cools or warms it to the temperature of the body, renders it fluid for its passage along the intestine, and secretes pepsin and hydrochloric acid for the first stage of protein digestion. In addition, it produces an internal secretion concerned with hæmatopoiesis.

Gastric Secretion. The acid secretion is produced by oxyntic cells in the simple tubular glands of the stomach wall, and, as Pavlov showed many years ago, the acid is produced in greatest amount at the cardiac end of the stomach, (whereas the secretion is neutral or even alkaline near the pylorus.)

The flow of acid juice is influenced by psychic stimuli and by various kinds of food—appetising meats and spiced foods cause a rapid outpouring of juice, whereas bread or albumen-water yields practically none. The concentration of acid, however, is maintained at a remarkably constant level, and variations in gastric acidity in health and disease depend principally upon departures from the normal process of neutralization. Neutralization is effected in health by many factors, but principally by the alkaline pancreatic juice. In normal circumstances there is frequent regurgitation of this fluid through the pylorus into the stomach, and when spasm or impaired pyloric control prevents this regurgitation the acidity is increased.

Gastric Motility. The motor functions of the stomach are concerned with the proper mixing of the food and with its despatch into the duodenum. The whole stomach is normally in a state of tone, the degree of which varies greatly even in health, and is naturally greater in those of sthenic build than in visceroplotic persons. The tone is interrupted at intervals by contractions, the most important of which are true peristaltic waves, which sweep across the stomach as far as the pylorus. On the fluorescent screen the waves appear to start at the mid-point of the stomach, and increase in depth and intensity as they progress. In the later stages of digestion, as the stomach empties, the waves appear at progressively higher points, so that eventually they may be observed to sweep over the whole organ. In addition to this peristalsis, the pyloric canal may exhibit another type of muscular activity, in which it contracts as a whole, independently of the rest of the stomach.

The discharge of gastric contents begins very soon after a meal, and at the end of from three to five hours the stomach should be empty.

Pyloric Mechanism. The action of the pylorus is of great importance in relation to gastric and duodenal disease. It regulates, on the one hand, the discharge of suitably prepared food into the duodenum, and, on the other hand, the proper regurgitation of alkaline juices into the stomach. The pylorus is guarded by a well-defined sphincter innervated both by the *vagus* and the sympathetic nerves, the former inhibitory, the latter motor in function. Normally, the pylorus is in a mild degree of tonic contraction, which is scarcely sufficient to close its lumen, and is easily overcome by increased pressure in the stomach or in the duodenum.

It was believed by Pavlov, and later by Cannon, that there is an "acid control of the pylorus," so that excessive discharge of highly acid chyme into the duodenum is prevented by reflex contraction of the sphincter. It has been shown recently, however, that the sphincter opens and closes whatever the chemical reaction of the contents may be, and even the direct application of hydrochloric acid through a duodenal tube does not necessarily cause the pyloric sphincter to contract. Radiological examination indicates that the sphincter relaxes usually at every third or fourth peristaltic wave, and that increased gastric acidity has only a slight retarding influence upon the emptying process.

Gastric and Duodenal Pain. Gastric and duodenal pain may be severe and incapacitating, yet the stomach and duodenum like other abdominal viscera are insensitive to direct stimulation, and when the abdomen is opened under local anæsthesia they may be cut, clamped or cauterized painlessly.

The pain of an ulcer occurs when gastric acidity is at its highest concentration, an hour or two after food, and for this reason it has been thought that the pain is due to the direct acid stimulation of exposed nerve endings. But similar pain may occur without ulceration and without hyperchlorhydria, in patients in whom no gross organic lesion is recognizable. It is not uncommon, for example, to find such pain in chronic appendiceal disease. For these reasons Hurst has suggested that the pain is not due directly to increased acidity, but rather to spasm or to stretching of the muscle fibres. In this way can be explained the rapid relief of pain which sometimes follows eructation, and it is possible that part of the virtue of such alkalies as sodium bicarbonate lies in stimulating eructation by the rapid liberation of carbon dioxide. Diminution of acidity no doubt assists to relieve spasm.

It is notable that a peptic ulcer may remain completely painless during long periods, though demonstrably not healed. This would suggest that the pain is mainly due to superadded inflammation. Kinsella quotes observations which show that whilst the normal stomach, exposed under local anæsthesia, is insensitive to pressure, manipulation of the stomach in the region of an ulcer is painful. He attributes the pain of peptic ulceration to congestion and consequent increased tension within the stomach wall.

PEPTIC ULCER

Peptic ulcers may develop on any portion of the alimentary tract exposed to the action of the gastric juice. The great majority occur in

the stomach and duodenum, and such gastric and duodenal ulcers will be described in detail in this chapter. It will not be out of place to mention at this point, however, that peptic ulcers of similar type occur also in the distal portion of the *œsophagus* (*see* p. 447), in the *jejunum* after the performance of gastro-jejunostomy (*see* p. 464), and rarely in other parts of the small intestines (*see* p. 497).

Acute Ulcer

It seems possible that all ulcers are at first acute. Acute ulcers may be single, but they are often multiple, and may occur in any part of the stomach or the duodenum. They arise from a variety of causes, and are common in the later phases of many acute infective and toxic conditions. The duodenal ulceration that follows extensive burns belongs to this category. Acute ulcers are round or oval, and at first they are mere erosions of the mucous membrane. If they extend they penetrate the deeper coats of the wall by progressive sloughing, which diminishes in extent as the ulcer deepens and gives the ulcer a characteristic terraced appearance. Acute ulcers are apt to erode arterioles, and to cause hemorrhage. (Less commonly they penetrate all the coats and perforate suddenly into the general peritoneal cavity.) Microscopically, there is often a striking absence of inflammatory change, and apart from some oedema the surrounding wall may show little deviation from the normal.

The great majority of acute ulcers undoubtedly heal rapidly within a few weeks of their onset and do not recur. Only relatively few persist, but this small proportion of chronic ulcers forms the bulk of those seen by the surgeon.

Chronic Ulcer

Chronic ulcers show a remarkable tendency to be restricted to certain very limited regions in the stomach and duodenum. In the

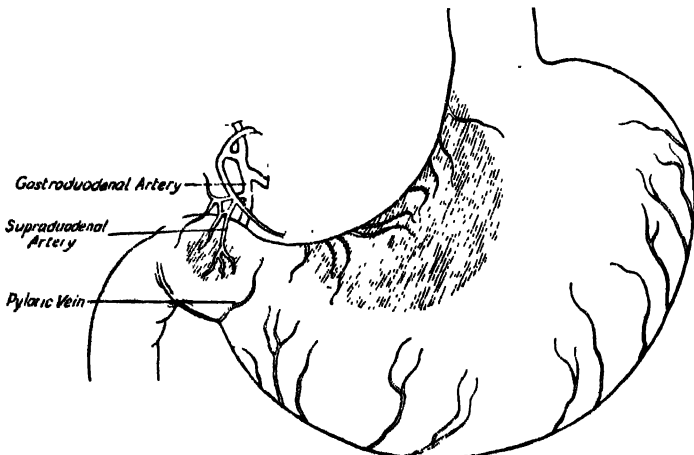


FIG. 204. Sites of peptic ulceration. The shaded portions indicate the sites of the great majority of peptic ulcers.

stomach the "ulcer-bearing area" includes the smaller curvature and the adjacent anterior and posterior surfaces, from the *œsophageal*

orifice to about $1\frac{1}{2}$ inches from the pylorus; in the duodenum the area affected is $\frac{1}{2}$ to 1 inch from the pylorus. It has been estimated that 90% of chronic ulcers are found in these situations. The pylorus itself is but uncommonly the site of ulceration (5% to 10%), and the great majority of so-called pyloric ulcers are actually situated in the duodenum. The greater curvature, fundus and cardia are only very rarely affected.

Two or more chronic ulcers frequently coexist. "Kissing" duodenal ulcers are common, and coincident gastric and duodenal ulcers are sometimes found. Failure to recognize such a coincident ulcer accounts for some of the unsatisfactory results of operation.

Frequency and Incidence. Surgical statistics show that chronic ulcers occur more commonly in the duodenum than in the stomach, and



FIG. 205. Duodenal ulcers. Two ulcers, characteristically small and rounded, are situated on the anterior and posterior wall respectively, about 1 cm. beyond the pylorus. The anterior ulcer has perforated.

that while gastric ulcer is equally common in the two sexes, duodenal ulcer is far more frequent in men than in women. Wilkie states that in 300 cases, the proportion of duodenal ulcer to gastric ulcer was 3.8 to 1, and duodenal ulcer occurred three times more commonly in males than in females. Ulcers are rare in childhood and adolescence, and the great majority occur in adult life, the incidence being greatest in the third and fourth decades. Ulcers are very common in Great Britain and North America and in certain parts of India, whereas they are extremely rare in certain other countries, notably China. This incidence is no doubt attributable principally to the dietary, which includes a high proportion of meat and highly spiced foods in the former countries, and is almost wholly vegetarian in the last-named country.

Morbid Anatomy. Duodenal ulcers are round or oval. Gastric ulcers, at first round, may spread from the smaller curvature, to assume a saddle shape, and may reach large size. The ulcer is surrounded by smooth mucosa which approaches or overhangs the crater. The

excavation has a regular, sharply defined edge, and its walls are vertical, extending steeply to the floor of the ulcer, so that often there is a typically "punched out" appearance. It is important to recognize that almost invariably there is a complete breach of the muscle coat, no trace of which is recognizable in the floor of the ulcer. The ulcer extends most frequently to the subserous layer, which is fibrous, oedematous and thickened. When the viscus is exposed at operation the only visible indication of the ulcer may be this thickened subserosa, stippled with numerous capillary vessels. In other cases, the external signs of an ulcer are more obvious; the peritoneum is puckered and scarred, oedematous tags of omentum cover it, and there may be adhesion to other organs.

When the ulcer is spreading, small sloughs extend beyond the margins of the crater, satellite acute ulcers appear in the neighbouring



FIG. 200. Chronic gastric ulcer, situated near the smaller curvature of the stomach, and invading the pancreas. Note the fibrosis and in-drawing of the surrounding mucous membrane. (After Cruveilhier.)

mucosa, and, in addition, a varying degree of catarrhal inflammation is present.

Microscopically, the floor and margins of the ulcer show the changes characteristic of a chronic inflammatory process. The crater is lined by necrotic material, and this is surrounded by dense fibrous tissue containing areas of lymphocytic or polymorph infiltration. Often there is a considerable degree of endarteritis obliterans, and this is of importance in diminishing the tendency to excessive hæmorrhage. Newcomb has drawn attention to another feature characteristic of chronic ulcers, namely, that the muscle fibres at the edge of the ulcer are spread out fanwise and eventually approximate to and fuse with the fibres of the muscularis mucosæ. At the margin of the ulcer the epithelium is distorted by the fibrous tissue, and the tubules of the mucosa are dilated and irregular in shape; this is a point of some importance, for the distortion and irregularity may simulate cancer.

Ætiology of Peptic Ulcer

Since peptic ulcer occurs only in those parts of the alimentary tract to which the gastric juice has access, it is clear that the immediate cause of the ulcer is erosion by peptic digestion. The normal mucous membrane is immune to such digestion; it follows, therefore, that the formation of an ulcer may result either from loss of this protective

immunity or from augmentation of the digestive activity of the juice.

It has been suggested that the mucous membrane is devitalized as a result of thrombosis in one of the end arteries of the stomach wall (Virchow) or of infection (Rosenow), but of this there is little evidence. On the other hand, there is a good deal of support for the view that increase in the digestive activity of the juice is at least one of the factors involved. Hyperchlorhydria almost invariably accompanies ulcer of the duodenum; in gastric ulcer it is not so common, but here the acidity may be masked by the gastritis which is commonly present.

Recent observations emphasize the importance of a constitutional predisposition to ulcer. A familial tendency is evident in over 10% of cases and is sometimes very striking. Draper has drawn attention to a special anthropometric type which he believes to be associated with the predisposition to ulcer, a type characterized by a particular facial conformation—a long narrow face with deeply etched naso-labial folds—and by certain special features of cranial shape.

But the clearest evidence of a predisposition is to be found in the nervous constitution or temperament of ulcer patients, who are commonly of the type described as vagotonic—lean, energetic, restless, over-conscientious. This tendency is most marked in duodenal ulcer; indeed it is quite exceptional to see a duodenal ulcer in any other type of person. In gastric ulcer the tendency is less clear.

The relation of peptic ulcer to nervous tension is supported by much clinical evidence; for example, the high incidence of ulcer in executives and professional men, the rapid relief of symptoms brought about by resting in bed or going on holiday, and the frequency with which relapses follow periods of emotional strain. In this latter connection, Davies and Stewart have shown that hamatemesis commonly follows shortly after acute worry over financial, domestic or family difficulties. Similarly it has been shown that the incidence of perforations is increased during periods of anxiety, for example in districts subjected to intense air bombardment.

These observations suggest that the cause of peptic ulcer is to be found in a disturbance of the innervation of the stomach. The stomach is supplied by both vagus and sympathetic fibres, and while their effects are by no means clear or distinct, it may be said, in general terms, that the action of the vagus is both motor and secretory, while that of the sympathetic is to antagonize these actions. Thus a preponderance of vagus stimulation leads to increased motility, with spasm, and to increased secretion, with hyperchlorhydria.

It is known, moreover, that the vagus centre in the hypothalamus is affected markedly by stimulation from the higher centres. In consequence the stomach is very sensitive to psychic and emotional influences. Pavlov's experiments on dogs submitted to sham feeding showed how the mere sight of food stimulated the secretion of gastric juice; while recently Wolf and Wolff, by observations on a man with a gastric fistula, have shown that not only the secretion but also the motility and vascularity of the stomach are influenced by nervous stresses. Indeed, it may be said that the stomach is the mirror of emotions; it may blush with shame or grow pale with rage, writhe in anger or stiffen

with fear. The importance of these reactions in relation to peptic ulcer needs no emphasis.

It seems probable that in a patient thus predisposed, the formation of the ulcer may be determined by a variety of factors—tobacco smoking, focal sepsis and the like. Somervell has suggested, on the basis of his experience in Travancore, that the mucous membrane may be devitalized as a result of vitamin deficiency; but in Great Britain and America, where ulcer is common in every social class, the influence of diet is probably very slight. The manner of eating, on the other hand, may be quite important. Ulcer patients commonly eat their food too hot and too quickly, and it may well be that the unmasticated coarse lumps traumatize the mucous membrane and thus render it liable to ulceration.

The precise localization of chronic ulcers to the "ulcer-bearing sites" (p. 454) provides further evidence of the importance of trauma as an aetiological factor. The lesser curvature and adjacent surfaces of the stomach constitute the principal food route or "magenstrasse" along which passes the great bulk of food entering the stomach, and this area is consequently subject to more than its share of wear or tear. Similarly, the duodenal ulcer-bearing areas are situated just where the wall is exposed to the full force of the highly acid chyme expelled through the pylorus.

Course, Complications and Sequelæ of Ulceration

A remarkable characteristic of chronic ulcers is the periodicity of the clinical features, phases of complete freedom from symptoms alternating with phases of discomfort. It is difficult to believe that the free intervals indicate temporary healing of the ulcer, but rather it would seem that they represent phases of quiescence. True healing of an ulcer of any considerable size can probably not be achieved under the most favourable circumstances in less than several weeks, and if extensive adhesions are present the period required must be longer still.

Hæmatemesis and Melæna. The occurrence of bleeding, in the form of a slow ooze from the raw surface, is very common, especially when the ulcer is in an active spreading phase, and the examination of the *fæces* for occult blood is an important part of the clinical investigation. More copious hæmorrhage occurs less commonly, giving rise to obvious melæna or to hæmatemesis, and may be so severe as to prove fatal.

According to Bulmer, more than 10% of cases admitted to hospital on account of hæmatemesis prove fatal.

Hæmorrhage may occur in either acute or chronic ulceration. In Bulmer's 578 cases there were 257 acute and 321 chronic. The more severe types of hæmorrhage are the result of chronic ulceration more often than acute, for the reason that the indurated fibrous tissue at the base of a chronic ulcer tends to prevent retraction of the bleeding vessel. It is important to note, however, that severe and even fatal hæmorrhage may take place from an ulcer so small as to elude careful search. This is a point of importance when the question of operative treatment is being considered.

Hæmorrhage from an ulcer is occasionally so profuse as to cause

death within a few hours. This is most likely to occur when a large vessel, a major branch or even the main stem of one of the arteries supplying the stomach, is eroded. More commonly, however, death occurs as a result of continued or recurrent but less profuse bleeding. The hæmorrhage may not have been copious initially, but is continued or recurs during several days or even a few weeks. In cases of repeated severe hæmatemesis, the mortality rate is over 50% (Davies and Nevin). In such cases, if the bleeding is not too profuse, the red cell count may be maintained at a moderately high level by mobilization of the red cells held in reserve in the bone marrow and spleen, and by rapid production of new red cells. The hæmoglobin, however, cannot be restored so rapidly, and the hæmoglobin content of the blood falls to 20% or even lower. This impairs the transport of oxygen, leads to tissue anoxæmia, and finally brings about a reduction of the alkali reserve (acidosis).

Penetration and Perforation. Ulcers on the posterior wall of the stomach or duodenum rarely perforate acutely, but rather tend to penetrate adjacent viscera that have become fixed to the stomach or duodenum by adhesions. The pancreas is the viscus most frequently penetrated, and the ulcer may extend deeply into its substance. In the neighbourhood of the ulcer the pancreas undergoes chronic inflammatory changes, but it is remarkable that acute pancreatitis is a rare complication, and that there is rarely any demonstrable deficiency of pancreatic function.

In a few cases a posterior ulcer penetrates towards the liver, or it may give rise to abscess formation in the omental bursa or in the subphrenic region. Rarely, a penetrating ulcer may open into the transverse colon, forming a gastrocolic fistula. An ulcer has even been known, in exceptional cases, to perforate into the jejunum, giving rise to a natural gastrojejunostomy.

Acute perforation into the general peritoneal cavity is now a common complication. It has not always been so. Until the close of the nineteenth century it was rare, but since then its frequency has increased progressively. Thus in Glasgow between 1924 and 1944 the disease has more than doubled in frequency. Moreover there has been a curious change in incidence. In the nineteenth century most perforations were gastric perforations and the majority affected women, especially girls aged from eighteen to twenty-eight years. Now duodenal perforations greatly exceed gastric (in the proportion of nearly seven to one), men are affected far more often than women (again nearly twenty to one) and the curve of age incidence is flatter, with most cases occurring between twenty-five and forty-five years. ((A perforated gastric ulcer is considerably more dangerous than a perforated duodenal ulcer, for the perforation is generally of larger size and the peritoneal cavity is flooded by large amounts of the highly irritating and sometimes infected gastric contents, whereas a duodenal perforation is usually small, and such fluid as escapes is less irritating.))

The ulcer may be an acute one of recent onset, but is far more often chronic, as indicated by the clinical history and by the naked-eye character of the ulcer. It is true that the clinical history obtained

during the agony of a perforation often makes no mention of previous indigestion, but careful questioning subsequent to operation will generally elicit a clear history of long-standing stomach trouble. In rare cases, a patient may suffer two or even three perforations, either of the same or of consecutive ulcers.

Perforation of an ulcer is due to sloughing of an unsupported portion of its floor, probably due in most cases to interference with its blood supply. Often the perforation is of large size, half a centimetre or even larger, rounded or oval and with a smooth, indurated margin. Less frequently the perforation is so small as to be classed as a "leak." Such a leaking ulcer is most commonly situated in the anterior wall of the duodenum. It permits the escape of a little fluid, which gravitates towards the right iliac fossa and may give rise to pain in that area.

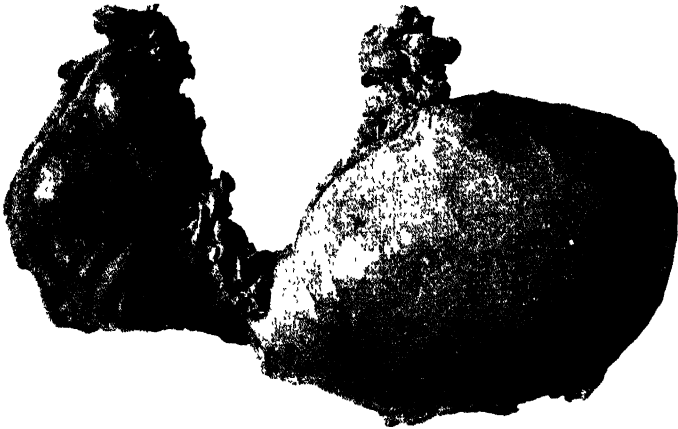


FIG. 207. Hour-glass deformity of the stomach, due to fibrosis round a chronic gastric ulcer.

(Museum of Royal College of Surgeons of Edinburgh.)

A leaking ulcer may become occluded by omental adhesion and remain healed, but more often it enlarges gradually and assumes the character of a complete perforation.

The peritonitis resulting from perforation of a peptic ulcer is at first often non-infective, and is due to the irritant action of the gastric or duodenal fluids. The peritoneal exudate may be sterile in nearly 70% of cases (Deaver and Pfeiffer). Owing to reflex inhibition of the secretion of acid gastric juice, however, organisms swallowed in the saliva or already present in the stomach proliferate rapidly, and in the later stages the peritonitis is predominantly infective in type.

Pyloric or Duodenal Stenosis. This is an end-result of chronic duodenal ulceration, and the stenosis may eventually progress to an extreme degree. Obstruction leads to hypertrophy of the gastric musculature and to dilatation of the stomach, and this may proceed till the viscus fills the greater part of the abdomen. The dilatation often affects particularly the pyloric antrum, and thus the obstructed stomach

is distended to the right as well as to the left of the mid-line. In extreme degrees of stenosis there may be almost complete stasis of the gastric contents for twenty-four hours or longer.

When such severe gastric stasis is present, special features may be added. There is great dehydration of the tissues, from loss of fluids by vomiting and from exudation into the hugely distended stomach. Later there are headaches, drowsiness, and even suppression of urine, so that the condition may be mistaken for the uræmia of late renal disease. Lastly, signs of muscular irritability may develop, culminating in tetanic contractions of the feet and hands—so-called carpo-pedal spasms. These features are now recognized to be manifestations of

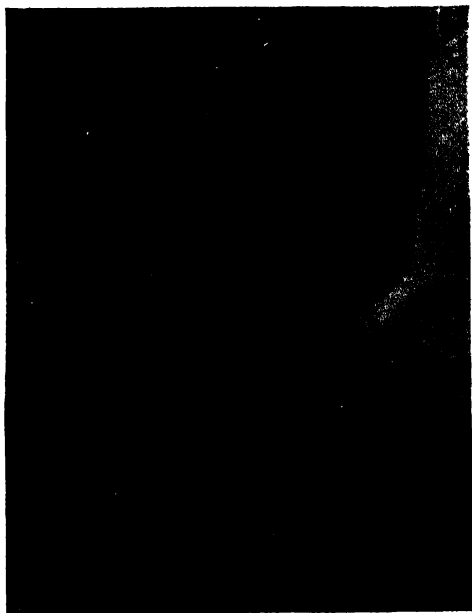


FIG. 208. Hour-glass deformity of the stomach, in a woman aged forty-three years. The contracture was due to a chronic gastric ulcer.

alkalosis, which is due partly to the dehydration and partly to loss of hydrochloric acid by vomiting and by combination with toxins.

Hour-glass Deformity. The great majority of examples of this deformity are the results of chronic gastric ulceration, but a few arise from malignant disease, or from perigastric adhesions. Exceptionally the deformity is congenital. Women are affected in more than 90% of cases. The contracture usually follows intramural fibrosis around an ulcer. It is usually situated nearer to the pylorus than to the fundus, and consequently the proximal sac is usually the greater. If the contracture is at a higher point the upper sac may be entirely concealed by the rib margin and may thus be overlooked during operation. The fibrosis has the effect of approximating the greater curvature at the affected point to the smaller curvature, and thus the orifice between the two sacs is never at the lowest point of the upper sac. This is clearly

seen in radiograms, in which the opaque meal gives a "water-spout" or "tea-pot" appearance. Not infrequently the ulcer heals, leaving a thin fibrous ring encircling the orifice. In other cases an active ulcer

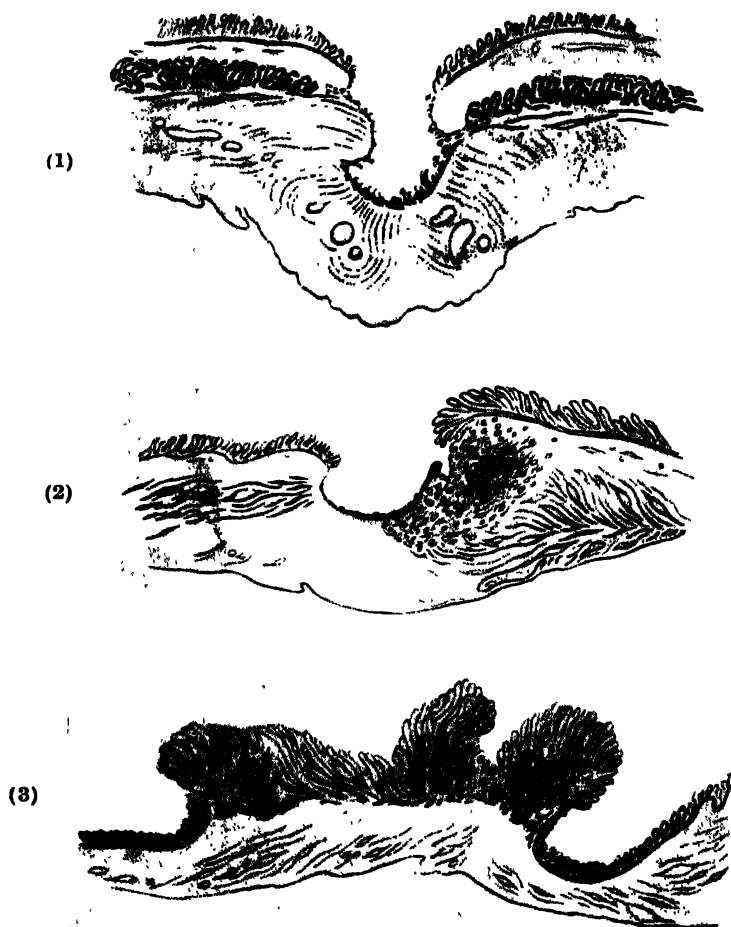


FIG. 209. Ulcer and Cancer of the Stomach. (1) Chronic peptic ulcer. The deep crater has penetrated the muscle coat, and its floor is composed of thickened, fibrous subserous coat. Note the large blood vessels embedded in fibrous tissue. (2) Ulcer-cancer. Malignant change in a pre-existing peptic ulcer. Epithelium from the mucous membrane at the edge of the crater is proliferating and spreading deeply. (3) Ulcerating cancer of the stomach. The crater is raised above the level of the mucous membrane. Its floor is composed of necrotic tumour tissue.

may remain, surrounded by a large inflammatory mass and adherent to adjacent structures. Quite commonly the hour-glass deformity is accompanied by pyloric stenosis—hence the lower sac may likewise become greatly dilated.

Malignant Change in a Chronic Ulcer. This change, the so-called

carcinoma *ex ulcere* or ulcer-cancer, may follow gastric ulcer but never duodenal ulcer.

It is important at once to distinguish clearly a carcinoma *ex ulcere* from a primary carcinoma in which secondary ulceration has taken place. The distinction is best made by cutting across the ulcer. A primary peptic ulcer of any considerable size has one very striking feature, namely, that it penetrates the muscular coat of the stomach and erodes a large circular gap in it. A primary carcinoma, on the other hand, though it penetrates and invades the muscle, does not destroy it entirely, and traces of muscular fibres may be recognized in its substance to quite a late stage (see Fig. 209).

Frequency of Malignant Change. The frequency of malignant change in gastric ulcer is a subject which in recent years has been much debated. It is obviously important from the therapeutic stand-



FIG. 210. Ulcer-cancer of the stomach. A large penetrating crater of a chronic ulcer is surrounded by an irregular, raised, indurated carcinoma.

(By courtesy of Mr. J. M. Graham.)

point, for an ulcer that might otherwise be considered suitable for medical treatment cannot justifiably be dealt with medically if it is likely to become malignant, and the same consideration obtains in the choice of conservative as opposed to radical surgical methods.

The estimates formed by different observers of the frequency of ulcer-cancer show wide variations, according to the criteria upon which the diagnosis is based. The problem may be approached from the pathological standpoint, either by examining peptic ulcers for evidence of malignancy or by examining carcinoma for evidence of old ulceration; it may be approached from the clinical standpoint by examining case histories and "follow up" records.

(1) A large proportion of chronic peptic ulcers contain near their margins small groups of atypical epithelial cells arranged in clumps or irregular tubules. Some pathologists have regarded these cells as evidence of early malignancy and have formed a high estimate of the frequency of ulcer-cancer. Others, however, look upon such atypical appearances as due to simple hyperplasia or to distortion by fibrosis, and their estimate is correspondingly much lower.

(2) When gastric carcinomata are examined the difficulty is to assess the evidence of pre-existing simple chronic ulcer. According to Newcomb, there are three histological criteria upon which this diagnosis can be based : (a) a complete gap in the muscle tissue of the stomach, (b) old-standing fibrosis in the base of the ulcer, (c) approximation or fusion of the muscularis mucosæ and the main muscle layer at the margin of the ulcer. Applying these criteria to 200 specimens of ulcer or carcinoma, Newcomb found six cases in which there was definite evidence of carcinoma originating in a simple ulcer.

(3) On the clinical side, the history of chronic dyspepsia in a case of gastric carcinoma is strong presumptive evidence that the growth has originated in an ulcer. Investigations from this standpoint have, however, given widely varying results.

More reliable figures may be obtained by following up the after-history of patients known to have a chronic ulcer. This has been done by Balfour, in cases subjected to the therapeutic test of conservative surgery. In his series of 1,280 cases, mainly treated by simple gastrojejunostomy, less than 6% eventually developed carcinoma of the stomach. Even in these cases, moreover, proof was lacking that the growth originated in the ulcerated portion of the stomach.

Since the observations of competent workers show such wide variations, it is difficult to form an accurate estimate of the frequency of ulcer-cancer. It is probably true, however, to say that most authorities believe that not more than 6% of chronic ulcers become malignant, and not more than 10% to 15% of gastric carcinomata arise from chronic ulcers.

Gastrojejunal and Jejunal Ulcer

Ulcers at or near the stoma constitute a particularly disturbing and troublesome complication of operations for peptic ulcer, and they are largely responsible for the dissatisfaction which, rightly or wrongly, has been felt in recent years in regard to this type of surgery.

Anastomotic ulcers occur nearly always in males, and as a complication of operations for duodenal ulcer. (They are rare following operations for gastric ulcer, and almost unknown in cases of gastric carcinoma.)

The frequency of anastomotic ulceration has been the subject of much controversy. It has been variously estimated as occurring after 1% or as many as 15% of gastric operations. The most reliable statistics are those of Walton, who followed up every one of 1,859 gastric and duodenal cases operated upon by himself. In this series, gastrojejunal ulcer developed thirty times, an incidence of 1.6%. In twenty-nine cases the primary operation was for duodenal ulcer, in the remaining case it was for gastric ulcer.

The type of primary operation most likely to be followed by ulceration at the anastomosis is gastrojejunostomy, but gastrectomy and the various types of gastroduodenostomy are not immune. In Walton's series, gastrojejunal ulcer occurred in 2.2% of the cases subjected to gastrojejunostomy and in 0.43% of those subjected to partial gastrectomy. It is generally thought that anterior gastrojejunostomy is

more liable to this complication than the posterior operation, although this view is not borne out by Walton's investigation.

Secondary ulceration is most likely to arise in the presence of that most important factor, an increased acidity of the gastric juice. The importance of this is demonstrated by the fact that in spite of the added neutralization afforded by the anastomosis, 70% of cases of gastrojejunal ulcer show persistent hyperchlorhydria. For this reason a patient with much hyperchlorhydria, being particularly liable to secondary ulceration, should not be submitted to gastrojejunostomy. There is some evidence to suggest that the hyperchlorhydria is a congenital, and perhaps a familial disorder. It is noteworthy that some



FIG. 211. Gastro-jejunal ulcer. A deep ulcer is seen immediately on the jejunal side of the anastomosis. Death resulted from hæmorrhage from an artery which can be seen at the right side of the crater.

(By courtesy of Prof. J. W. S. Blacklock.)

patients are particularly prone to develop anastomotic ulcers, whatever the type of operation performed. They may develop new ulcers successively after repeated operative interference.

Formerly it was usual to attribute an important rôle in the formation of anastomotic ulcers to local agents resulting directly from the operative procedure, *e.g.*, torsion or other malposition of the jejunal loop, clamp trauma, the occurrence of a hæmatoma at the suture line, or the irritation of an unabsorbable silk thread. Some of these possibly play a part in a few cases, but their importance is undoubtedly much less than was at one time thought. Other predisposing factors include those which have been mentioned in connexion with the ætiology of peptic ulcer in general, namely, infective foci, tobacco, highly acid foods, irritant foods and irregular meals.

Gastrojejunal or jejunal ulcers may occur at almost any period after operation, from a few weeks to several years. In a large proportion of patients in whom this complication develops it is possible to obtain a history of pain in the immediate post-operative period, and it seems likely that the great majority of ulcers originate then—a point which emphasizes the need for careful post-operative diet and alkali treatment. Ulcers that first give rise to symptoms later than four years after operation are uncommon, although there are cases on record in which the symptoms appeared as late as fourteen years after the original operation.

The ulcer may be situated either near the anastomosis, at its margins or in the jejunum at some distance from the opening. The majority about on the line of anastomosis, either on its gastric or jejunal side and the suture line forms one margin to the ulcer. According to Walton, jejunal ulcers remote from the anastomosis are exceptional. When they occur they are situated in the jejunum directly opposite, or a few centimetres down the efferent loop, but very seldom in the afferent loop, owing to the alkalinity of its contents. In its life history the ulcer resembles a chronic gastric or duodenal ulcer, and is equally apt to bleed and to perforate into the general peritoneal cavity. It possesses a somewhat distinctive feature, however, in a special tendency to adhere to neighbouring structures, especially the mesocolon, and to form a large inflammatory mass round a relatively small crater. The ulcer is moreover apt to implicate adjacent viscera, particularly the colon, and eventually to perforate into it, with the formation of a fistula. The fistula may be between the stomach and the colon—*gastro-colic fistula*; between the anastomosis and the colon—*gastro-jejunocolic fistula*; or between the jejunum and the colon—*jejuno-colic fistula*. The development of a fistulous communication with the colon is suggested by the discomfort which may ensue from one or other or a combination of such symptoms as foul eructation or faecal vomiting, diarrhoea, and wasting. It is noteworthy that when the fistula is well established pain may be lessened or disappear as there is a tendency for the ulcer to heal. The fibrosis consequent on the healing of the ulcer may be responsible for obstruction at the stoma or in the colon.

Pathological Complications of Operations for Ulcer

Of all the operations that have been advocated for peptic ulceration the most widely adopted has been some form of gastrojejunostomy, either by the older anterior or, more commonly, by the posterior method. One disadvantage of this operation, remarkably enough, is the great ease with which it may be performed, and in former years this led to its use in a large number of cases for which it was entirely unsuitable. To this, as well as to faulty technique, are attributable the complications, which, though rare in comparison to the number of operations performed, are so distressing as to have been responsible for the aphorism, “gastro-enterostomy—a disease.”

Reference has already been made to the occurrence of secondary ulceration at the anastomosis, which may follow gastrojejunostomy or

other forms of short-circuiting operation. Hæmorrhage from a vessel at the line of suture, leakage of infective matter into the peritoneal cavity (a remarkably rare event), excessive formation of adhesions, and other complications which are not peculiar to this type of operation, need merely be mentioned. A complication of some frequency is *pernicious vomiting*, which may be associated with a so-called "vicious circle." It is probably due most often to an improper choice of operation, for instance, to the performance of gastrojejunostomy where no gross organic lesion exists, or where some condition such as a duodenal ileus remains unrecognized, but it may arise from errors in operative technique, when it is actually a manifestation of a form of high intestinal obstruction. In this latter type there is bilious vomiting, which may commence within a week of operation and be so severe as to prove fatal. More often, however, the onset is longer delayed and the obstruction takes a chronic or intermittent form.

The technical defects that occasion this complication are varied, but most commonly there is angulation or kinking of the afferent or efferent jejunal loop or even of both. Angulation of the afferent loop is likely to occur if this loop is made unduly long, when it forms a reservoir for bile and pancreatic secretion, the weight of which, by dragging on the stoma, aggravates any existing obstructive element; the contents of the loop, forbidden exit *viâ* the stoma, are regurgitated through the pylorus. Obstruction at the anastomosis may occur when the transverse colon and its mesentery are unduly short, a condition especially likely to be found in obese subjects, and the making of an inadequate aperture in the mesocolon may have a similar effect. In other cases, and particularly where the stomach is small and tonic, the jejunal loop is drawn up into the omental bursa and is thus kinked. Lastly, obstruction may result from less common causes, such as torsion of the jejunum during the suturing process, or even volvulus of the afferent loop around the fixed point of the anastomosis.

An occasional complication of posterior gastrojejunostomy is herniation of a loop or even of the whole of the small intestine into the omental bursa. The resulting symptoms may be very acute and rapidly fatal, or they may be chronic or intermittent. Somewhat similarly hernia may occur between the afferent loop and the transverse mesocolon. In this case the intestine remains in the greater peritoneal sac. Even more rarely intussusception of the afferent jejunal loop into the stomach may occur, and retrograde intussusception of the efferent loop has also been described; in instances of this last complication the gastric acidity has usually been very high, and it may be presumed that violent antiperistaltic waves have been excited by this irritation.

CARCINOMA OF THE STOMACH

This is one of the commonest of new growths in man, and from its malignancy, its insidiousness of onset, and its deep-seated situation, it is one of the most difficult to eradicate. It occurs most commonly between the ages of forty and sixty, though occasionally it may be found

much earlier in life. The male sex is affected more often than the female, in the proportion of 3 to 2.

It is generally believed that there are two important predisposing factors—chronic gastritis and gastric ulcer. The views held in regard to the relationship of gastric ulcer to carcinoma have already been discussed, and it will be sufficient to state here that such a relation can only be demonstrated in a small proportion, perhaps 10% to 15% of cancers.

Chronic gastritis is doubtless a more common predisposing cause, and indeed some authorities claim that it is an almost invariable ante-

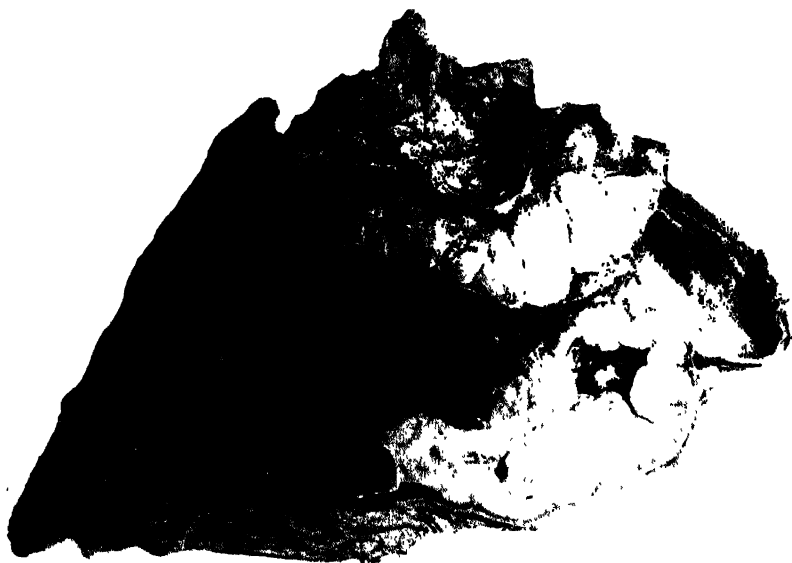


FIG. 212. Carcinoma of the stomach (seen from behind). The growth has originated near the pylorus and has spread thence, encircling and constricting the pyloric antrum.

(Department of Surgery, University of Edinburgh.)

cedent of carcinoma. Chronic gastritis is probably responsible for the achlorhydria characteristic of carcinoma of the stomach.

There are some interesting differences between the incidence of carcinoma of the stomach in different countries. In Great Britain, carcinoma of the stomach accounts for 22% of all types of cancer in man, as compared with 42% in America, 55% in Holland, Bavaria and Spain, and 66% in Czechoslovakia. According to Hurst, the differences in this country and Holland are mainly accountable by dietetic habits, for work done under his supervision appears to show that the Dutch smoke more, consume more alcohol and spiced and overheated foods, chew their food insufficiently and eat it too quickly. Oral sepsis, which is also more common in Holland than in this country, may be another predisposing factor.

It is usual to describe four principal varieties of gastric cancer: (1) the sessile or ulcerating, (2) the polypoid or proliferative, (3) the

colloid or mucoid, and (4) the atropic or leather-bottle. The fourth variety, though rare, is such a distinctive one as to be regarded separately, but it should be clearly recognized that the others are not so much distinct diseases as deviations from a common type. The great majority of gastric carcinomata are intermediate forms having some of the characteristics of all. A fifth type of growth requires also to be mentioned, a squamous-cell carcinoma, which is occasionally found at the cardiac end; it may be derived from the lower end of the œsophagus or from heterotopic œsophageal mucous membrane in the stomach close to the cardia.

(1) **The Sessile or Ulcerating Form.** This is the most common type of growth, and is also the most malignant, for it is usually symptomless



FIG. 213. Carcinoma of the stomach. The growth, which has originated near the smaller curvature, forms a massive tumour projecting into the cavity of the stomach. Note the hypertrophy and "fragmentation" of the muscle coat.

(By courtesy of Mr. J. M. Graham.)

in the early stages, it infiltrates widely, and soon gives rise to metastases. It occurs principally in the pyloric region and at the smaller curvature, though no part of the stomach is exempt. The growth is of a scirrhus nature, hard and fibrous. At first it is confined mainly to the mucous and submucous coats, extending widely in these planes; later it penetrates the muscularis to reach the peritoneal aspect. The surface of the growth is usually ulcerated, with a shallow crater lined by necrotic malignant tissue and with hard, raised, rolled margins.

Microscopically, growths of this type are composed of spheroidal or sometimes columnar epithelial cells in a well-formed fibrous stroma. The epithelial cells may be arranged in irregular tubules or acini but are often scattered irregularly in small groups. To this latter type the term "carcinoma simplex" has sometimes been applied.

(2) **The Polypoid or Proliferative Form.** This is a less common type.

It forms a bulky, soft, cauliflower-like mass which projects into the stomach. When situated towards the pylorus it tends, in virtue of its bulk, to cause some obstruction early in the disease. The superficial part of the growth rapidly degenerates and local surface ulceration occurs, leading to frequent hæmorrhage, to secondary infection, and to early cachexia.

Microscopically, this type of growth is usually composed mainly of columnar cells, arranged principally as irregular tubules or acini; but spheroidal cells also are found. The tumour is often soft or "encephaloid," with a scanty, poorly formed stroma, and degenerative changes are common.

(3) **The Colloid or Muroid Form.** This variety also occurs as a rule in the pyloric region. It is somewhat rare, and is usually regarded as a

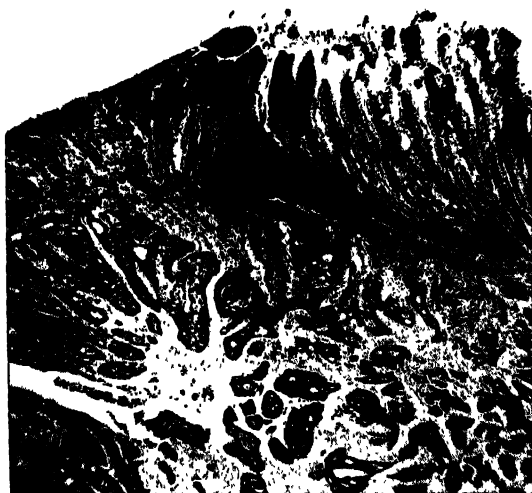


FIG. 214. Cancer of the stomach. The tumour is composed of spheroidal and columnar cells in an irregular acinar formation.

(Department of Surgery, University of Edinburgh.)

form of degenerative change rather than a special type, but its characteristics are sufficiently distinctive to merit separate description. The tumour on section has a peculiar translucent appearance. A characteristic feature is the tendency of the growth to extend to the peritoneal surface. Adjacent structures are invaded, and the liver, spleen and other organs may be glued together by a thick casing of gelatinous material. Microscopically, the striking feature is the large amount of mucoid material, which is situated both inside the malignant cells and in the stroma. Large globules fill the cell protoplasm and displace the nucleus to one side, giving an appearance comparable to a signet ring. The same appearance is present in metastases.

(4) **The Atrophic or Leather-bottle Form.** This is a slow-growing carcinoma which spreads entirely in the wall of the stomach, only invading lymph glands and distant structures at a very late stage. It is characterized by the presence of much fibrous tissue. Beginning

usually in the pyloric region, it extends proximally and may eventually implicate the whole stomach from the pylorus, to the cardia (*see* Fig. 215). In an extreme case, the stomach is greatly contracted, and its capacity may be reduced from the average normal content of one to two pints to a few ounces. The wall is diffusely indurated, sometimes measuring 2 cm. or more in thickness, and on its serous aspect it is pale and almost pearly white. The mucous membrane is rugose, and is often œdematous, congested, and altered by secondary catarrhal changes. In a considerable proportion of cases there is an ulcerated area, often in the pyloric region, and it is usually presumed that this indicates the site of origin. On cross section it is seen that the thickening affects principally the sub-mucous and subserous coats, which are infiltrated with dense fibrous

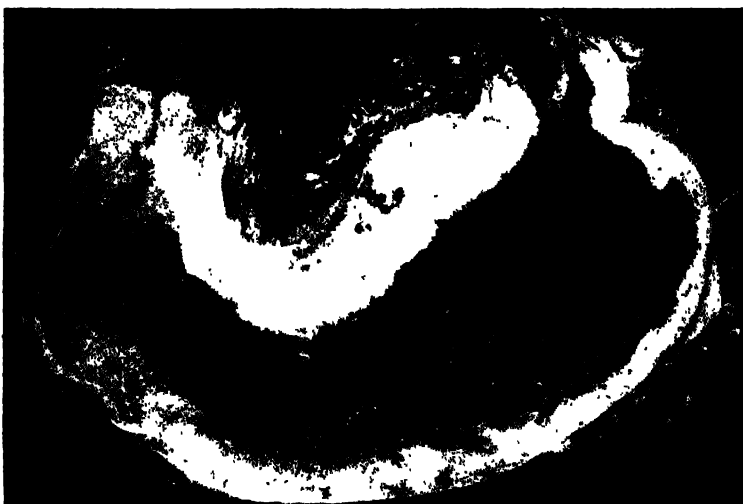


FIG. 215. Leather-bottle carcinoma of the stomach. The stomach is of small size and the whole of its wall is infiltrated and greatly thickened. The mucous membrane is œdematous, and being redundant it is thrown into folds.

(Department of Surgery, University of Edinburgh.)

tissue. The muscular coat presents a striking appearance, for the circular coat is greatly hypertrophied, and its fibres are, in addition, traversed by dense white bands connecting the submucous and subserous layers, an appearance often described as segmentation of the muscle. Although such great contraction and thickening of the wall is present, there is no stasis, but on the contrary food passes into the duodenum with great rapidity.

Microscopic examination shows that the cancer cells are scanty, and buried in fibrous tissue, so that examination of several sections may be necessary before the malignant nature of the condition can be determined. The cells are spheroidal, and are scattered through the tissues in small clumps rather than arranged in definite masses or alveoli.

At a late stage of the disease metastases occur in the regional lymph glands as well as in the liver and more distant situations, but for a long time the carcinoma remains limited to the stomach. If technical con-

siderations warrant the operation, complete excision is indicated, and this is the only disease for which total gastrectomy is justified.

Spread of Gastric Carcinoma

In any of the types just described the disease spreads at first and principally by the lymph channels within the stomach wall; but in most cases, except in the "atrophic" form, at a relatively early period it reaches neighbouring lymph glands. Later, the adjacent viscera and

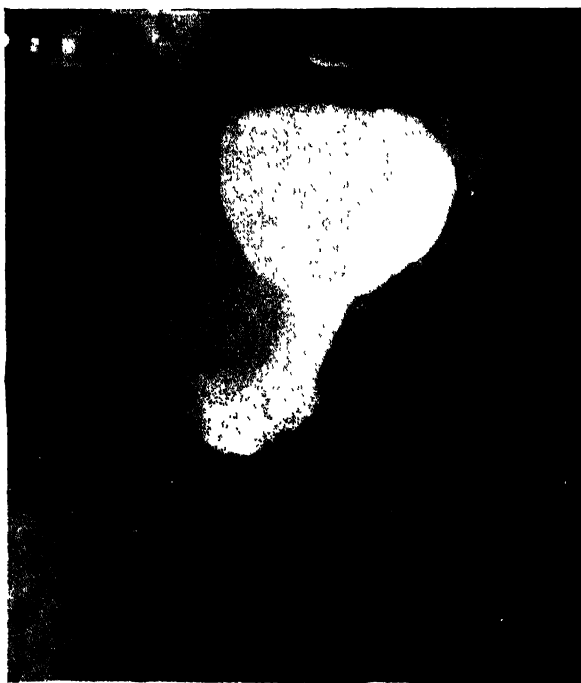


FIG. 216. Infiltrating carcinoma of the stomach. A radiogram after the administration of barium. The stomach is greatly reduced in size and narrowed by the infiltrating growth.

tissues are invaded by direct extension, and dissemination may take place through the peritoneal cavity and by the blood stream.

(1) *In the Stomach Wall.* This early spread, most obvious in the infiltrating or leather-bottle type, is nevertheless extensive and important in the other forms and in particular in the scirrhus, ulcerating type. The submucous layer may be infiltrated with pale-white streaks of malignant growth far beyond the limits of the actual ulcer, and around this visible zone is an even more extensive microscopic spread.

When the tumour is situated on the smaller curvature, the submucous extension is chiefly in the direction of the cardia, and around the anterior and posterior surfaces. Sometimes the cardiac orifice is involved, and secondary œsophageal obstruction results. The growth rarely

encroaches upon the pyloric ring, and the duodenum is only likely to be invaded from a secondary nodule implanted on its serous surface.

(2) *To Lymph Glands.* Metastases in lymph glands frequently appear at a very early stage of the disease. The first to be affected are usually the glands nearest the tumour and, from the usual situation of the tumour on the smaller curvature near the pylorus, two groups in particular are liable to early involvement. These are (a) the lower coronary group, situated between the layers of the small omentum close to the distal part of the smaller curvature, and (b) the pyloric and subpyloric group, which are placed close to the first part of the duodenum and in the angle between it and the head of the pancreas.

From the lower coronary group the growth tends to spread to the upper coronary group (rarely these may be the first to be involved) and thence to glands along the coeliac artery and to the para-aortic chain. The growth may extend in retrograde manner from the coeliac artery to reach the lymph glands in the porta hepatis, whence the liver may be affected.

From the pyloric and subpyloric glands the disease may extend to the supra-pancreatic glands and glands at the root of the mesentery. A malignant mass in the last situation may compress the third part of the duodenum and lead to duodenal obstruction.

If the primary growth lies near the greater curvature it tends to spread to lymph glands of the gastro-epiploic chain, between the layers of the gastrocolic ligament and in the great omentum. Such spread is less important, however, for these glands in turn drain back into those of the subpyloric group.

(3) *To Adjacent Organs.* The primary growth may extend directly into the pancreas, omentum or liver. Less commonly, there is invasion of the spleen and the colon, and occasionally of the jejunum.

(4) *By the Peritoneal Cavity.* When the growth has extended to the serous surface of the stomach, malignant cells are liable to be set free and to traverse the peritoneal cavity. Here they may give rise to numerous widely scattered metastases, at first small, like tubercles, and later growing extensively, or they may result in one or more large masses. These massive peritoneal metastases are particularly apt to arise in the great omentum, on the pelvic floor, or on the surface of one or both ovaries. In any of these situations a large secondary mass is liable to be regarded as a primary growth, particularly as the primary growth in the stomach may be almost symptomless.

(5) *By the Blood Stream.* This usually occurs at a late stage of the disease, but in young subjects may take place early. The liver is affected first; later, metastases are found in the lungs, brain, bones and other viscera.

SARCOMA OF THE STOMACH

Sarcoma may arise in any of the connective tissues of the stomach wall. It is of rare occurrence, constituting about 1% of all gastric tumours. It may develop at any time of life, but generally at an earlier age than carcinoma. The average age is about forty.

The tumour differs in no essential respect from a sarcoma elsewhere. It forms a large mass, which undergoes central necrosis early, and forms an extensive ulcer from which free hæmorrhage may occur. Secondary infection leads to rapid cachexia and death. The commonest form is a lymphosarcoma, arising in the lymphoid tissue of the submucous coat. Sarcoma sometimes arises in a leiomyoma. Round-cell and spindle-cell sarcoma also are described.

The tumour is situated most often in the pyloric antrum, but is rarely so close to the pylorus as to cause early stenosis. Achlorhydria is usually present, but this is by no means invariable. It is a remarkable fact that occasionally there is little loss of weight until the late stages of the disease.

Atypical forms of *lymphadenomu* (Hodgkin's disease) occasionally give rise to a large mass in the stomach wall, and this may progress in much the same way as sarcoma.

SIMPLE TUMOURS OF THE STOMACH

Gastric Polyposis. Polypoidal projections of the gastric mucous membrane are common near the margins of a gastric carcinoma, but the term gastric polyposis is restricted to a comparatively rare condition of simple papillomatous overgrowth. The polypi are papillary adenomata which arise in the mucous membrane and project into the cavity of the stomach. They are usually multiple, but single polypi have been reported. A rare form of polypus is that in which a limited area of the gastric mucosa is affected in a diffuse fashion, being raised in a well-defined velvety plaque in an otherwise healthy stomach.

At operation a group of polypi may be felt inside the stomach as a soft doughy or worm-like mass. The mucosa is covered with velvety red projecting masses, which vary in size up to that of a cherry, and are widely distributed, either in the pyloric portion or through the whole stomach. Ulceration and secondary infective changes are common, and often there is some catarrhal gastritis. Microscopically, the tumours are papillary adenomata, composed of columnar cells arranged in well-formed acini and supported by a lax connective-tissue stroma. In the diffuse plaque-like variety the tubules of the growth resemble the duodenal glands of Brünner. Gastric polyposis is very liable to be mistaken for carcinoma; the ulcerated surfaces bleed readily and a severe degree of secondary anæmia sets in; catarrhal changes reduce the gastric acidity, perhaps to zero; the vomit contains blood, mucus and even lactic acid; and on radioscopic examination the barium shadow is interrupted by numerous filling defects. In many of the reported cases carcinoma has supervened, but there does not appear to be that intimate relation between the two conditions which is found in the colon.

Other simple tumours of the stomach are rare. A myoma occasionally is found. It may project into the lumen, or subperitoneally, and in either event forms a smooth rounded or nodular lump, often of considerable size, and often pedunculated. Cases have been reported in which such a tumour has caused symptoms from pressure. When

it projects towards the lumen the tumour may ulcerate and simulate a malignant neoplasm, or it may be propelled towards the pylorus and cause obstruction at that point, or even intussusception. Rarely the presence of a large tumour has led to volvulus of the stomach.

Fibroma, lipoma, and angioma of the stomach may occur.

SYPHILIS OF THE STOMACH

Syphilitic affections of the stomach are uncommon, and of interest chiefly from their mimicry of carcinoma. They occur as late tertiary manifestations of the acquired disease, and begin as a gummatous infiltration of the submucosa, usually on the smaller curvature towards the pylorus.

The disease may progress to the formation of single or multiple gummatous ulcers or submucous nodules, or it may lead to extensive fibrosis of the affected part of the stomach wall.

In some cases a large gumma forms, softens in the centre and breaks down, giving rise to a large ulcerating mass resembling an ulcerating carcinoma. More commonly, syphilis leads to diffuse fibrosis of the stomach wall. If this occurs in the region of the pylorus, pyloric stenosis is the natural result; if in the body of the stomach, an hour-glass deformity. Rarely syphilitic fibrosis affects the greater part, or even the whole of the stomach, and gives rise to a condition readily mistaken for "leather-bottle" carcinoma or for fibromatosis of the stomach.

The clinical effects of syphilis of the stomach may resemble those of gastric ulcer or carcinoma. Hæmorrhage from the ulcerated surface, manifest in hæmatemesis or melæna, leads to severe anæmia, and there may be marked cachexia. Secondary catarrhal gastritis leads to excessive production of mucus, and in 85% of cases to complete achlorhydria. The diagnosis is rendered difficult by the fact that the disease often fails to respond to ordinary anti-syphilitic measures.

TUBERCULOSIS OF THE STOMACH

Tuberculous affections of the stomach and duodenum are extremely rare, a remarkable fact considering that the tubercle bacillus can survive exposure to gastric juice for several hours, and considering that infection of the lower alimentary tract from swallowed sputum is so common.

The most frequent tuberculous lesion is a single ulcer on the smaller curvature towards the pylorus; it has the characteristics of a tuberculous ulcer elsewhere, and has no distinctive clinical features. Occasionally several small miliary ulcers are present. Rarely a hyperplastic type of the disease occurs, with much fibrosis and little or no caseation; this variety at the pylorus may lead to stenosis and, as at the ileocæcal region, it may simulate carcinoma.

Tuberculous disease in the stomach is generally believed to follow infection from swallowed sputum; rarely a caseous lymph gland may adhere to the stomach wall and thus infect it.

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

A disease of the early weeks of life, affecting boys four times more frequently than girls, and especially prone to attack the first-born of the family. The muscular wall of the pyloric canal is hypertrophied, and this leads to narrowing of the lumen and obstruction. Distally, the hypertrophy is clearly delimited, for it never goes beyond the pylorus. Proximally, the limitation is less exact and the hypertrophy gradually diminishes until at the incisura angularis the muscle is of normal thickness. At the pyloric canal the swollen muscular wall forms a rounded bobbin-like mass. The circular muscle is particularly affected, and its fibres are pale compared to those of normal muscle, grey or

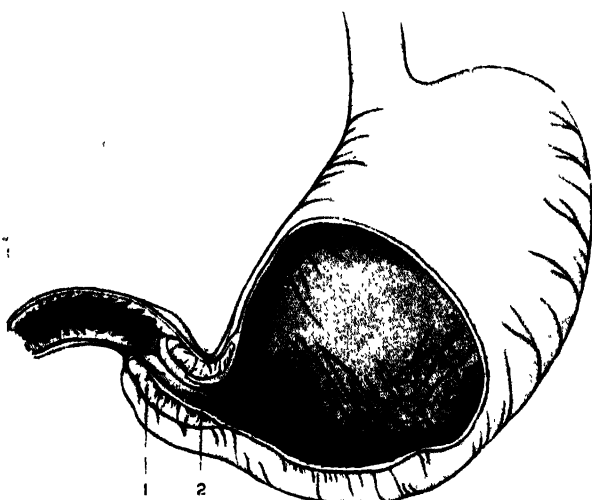


FIG. 217. Congenital hypertrophic pyloric stenosis, from a male, aged five weeks. Note (1) the great hypertrophy of the circular muscle fibres, (2) the fold of redundant mucous membrane. The stomach is greatly dilated.

greyish-white and poorly supplied with blood. Partly owing to the muscular overgrowth and partly owing to redundancy of the mucous membrane, which becomes folded upon itself, the lumen of the pylorus is greatly reduced. The stomach, and even the œsophagus, hypertrophies in efforts to overcome the obstruction and causes vigorous peristalsis, as is readily seen if the infant is examined during a feed. Later the stomach dilates and its mucosa undergoes secondary catarrhal changes.

Congenital pyloric stenosis is an inherited abnormality of recessive type, while sex and primogeniture are also determining factors. The underlying cause is the possession of a pair of abnormal genes, one from each parent, and should the recipient chance to be a boy and first-born, his chance of being affected is the Mendelian ratio 1 in 4. Girls and subsequent children are much less likely to be affected.

There have been numerous theories as to the significance of the pyloric lesion. Hirschsprung and Cautley maintained that the primary lesion is a congenital muscle hypertrophy, and that the pyloric obstruction is due to the increased thickness of the muscle and to the resulting spasm. John Thomson, on the other hand, suggested that the primary factor is a want of neuro-muscular coordination, which leads to functional obstruction at the pylorus, and to compensatory hypertrophy of the muscle fibres of the pyloric canal.

The clinical features are characteristic. The first sign usually appears within a few days or weeks of birth, when the baby, previously healthy, commences to vomit; the vomiting becomes forcible and projectile, from extreme muscular activity, and tends to occur within a few minutes of the beginning of a feed. The onset thus differs from that of congenital intestinal atresia, which is manifest from birth, and the vomit differs from that of volvulus of the mid-gut loop (*see p. 484*) in containing no bile.

There is another rare form of pyloric stenosis in children, due to a congenital defect—the stenosis of Landerer and Maier. The obstruction in this case is due to a diaphragm of mucous membrane at the pylorus, pierced by a very small hole. The symptoms in this type do not begin until later childhood.

VOLVULUS OF THE STOMACH

This rare accident may involve the whole stomach, or its pyloric portion alone. The partial variety generally occurs as a complication of hour-glass deformity, for in this condition the lower pouch, slung between the contracture and the pylorus, is relatively free to rotate. The complete variety is most likely to occur in association with diaphragmatic hernia, a benign gastric tumour, or of perigastric adhesions. In some cases the only predisposing factor is gastroptosis.

The volvulus may take place round an axis passing through the two orifices of the stomach, or one perpendicular to this line. In the former, organo-axial type, the greater curvature generally passes forwards and upwards, and comes to lie under the anterior part of the diaphragm. The transverse colon may be drawn upwards with the greater curvature and become impacted under the diaphragm. In the latter, mesenterio-axial type, the pyloric part of the stomach passes forwards, upwards and towards the left in front of the body of the stomach, carrying the right colic flexure with it. In this type the volvulus is generally of limited extent.

The main effect of volvulus of the stomach is to cause complete obstruction of the pylorus, and in some cases of the œsophageal orifice. There is little interference with the blood supply to the stomach. The stomach becomes greatly distended, causing severe epigastric pain and extreme collapse. Large quantities of fluid are lost into the dilated viscus, and dehydration is consequently a marked feature. If the œsophageal orifice is obstructed there is no vomiting, and attempts to pass a stomach tube are unsuccessful. In some cases secondary obstruction of the colon is a complicating feature.

ACUTE DILATATION OF THE STOMACH

This is a remarkable condition in which for no obvious reason the stomach becomes rapidly ballooned with gas, so that it fills the greater part of the abdominal cavity. Generally it is a post-operative complication, but it may follow simple manipulations, such as the application of a plaster case, and rare cases have been recorded in which it arose from no obvious cause in otherwise healthy young adults. The predisposing operation is most commonly an abdominal one, performed for affections of the female pelvic organs, the appendix, or gall bladder. It is curious that operations on the stomach itself practically never predispose to it. There appears to be no relation between acute gastric dilatation and infections.

Acute post-operative dilatation of the stomach rarely becomes manifest later than forty-eight hours after operation; sometimes it occurs within a few hours, and in a few recorded instances it has occurred actually during the operation. These cases are of particular interest; the stomach is suddenly observed to be increasing in size, and within a few minutes it fills the greater part of the abdomen and projects at the wound; after passage of a stomach tube a quantity of gas, of the composition of atmospheric air, is released, and the stomach immediately returns to its normal size.

The stomach may reach to the brim of the pelvis, its wall becomes greatly thinned, the mucosa eroded; and the gas later becomes replaced by foul, blood-stained fluid. The dilatation may be limited to the stomach, but this is unusual, and it commonly extends to some point in the second or third parts of the duodenum or even to the proximal coils of the jejunum. In about a quarter of the recorded cases the dilatation stopped short at the point where the duodenum is crossed by the superior mesenteric vessels (gastro-mesenteric ileus).

The cause is not fully understood. It is, however, generally agreed that the stomach is affected first and principally, and that duodenal dilatation, when present, is a secondary phenomenon, due to compression of the root of the mesentery from the drag of displaced small intestine. A healthy stomach when distended empties itself by the forcible expulsion of gas along the œsophagus, and it must therefore be presumed that before dilatation can occur there must be paralysis of the gastric musculature, and possibly also spasmodic contraction at the cardia; these predisposing affections may possibly arise from toxic changes in the muscle, but their sudden onset suggests rather a reflex action. The gas which fills the stomach might be thought to arise from the fermentation of intestinal contents, but this could hardly explain the extreme rapidity of the dilatation. McIvor has shown that in the cat some degree of gastric dilatation may be brought about by inserting a valvular tube into the upper part of the œsophagus, allowing air to be sucked down into the stomach but preventing its exit, and it is possible that some valvular mechanism may occur in man.

The effects of acute dilatation are immediate, grave, and sometimes fatal. In part, they arise from the mere distension of the stomach,

which displaces other viscera, pushes up the diaphragm and interferes with the action of the heart. Even more important, however, is the subsequent outpouring of fluid into the dilated viscus, for the tissues become dehydrated, the secretion of urine diminished, and alkalosis rapidly develops. If the duodenum is obstructed the effects of a high intestinal obstruction are superadded. It is not surprising that there is rapid collapse and great dehydration; at first there may be no vomiting, but later an overflow regurgitation may occur. Fortunately if recognized early the condition is amenable to treatment by passage of the stomach tube.

CHRONIC DUODENAL ILEUS

Chronic obstruction of the duodenum may arise from one of several causes, which fall naturally into two principal groups. The first group is that in which some gross obstructing lesion is demonstrable, for



FIG. 218. Chronic duodenal ileus. The transverse colon has been drawn up and the peritoneum incised, to show the third part of the duodenum, which is greatly distended. The root of the mesentery containing the superior mesenteric vessels is seen immediately to the medial side of the distended duodenum.

instance, calcified tuberculous lymph glands, or infiltration of the mesentery by malignant disease, or rarely, adventitious adhesions in this region. The second group includes those in which there is no definite organic disease to account for the obstruction.

The second group occurs most often in females and usually in those of viscerotonic habitus, but it may rarely be found in those of sthenic build. The obstruction is situated usually at the point of crossing of the superior mesenteric artery, and it is generally attributed to the pull of these vessels associated with a greater or less degree of prolapse of the small intestine (arterio-mesenteric ileus). In some cases

it appears as though displacement of the small intestine and consequent mesenteric traction is due to primary dilatation of the stomach or to gastropptosis. Rarely the obstruction appears to result from traction by the proximal colon upon the right colic artery, which crosses the third part of the duodenum obliquely. Very often it is not possible to demonstrate any obstruction, and the dilatation is merely part of a general visceroptosis. Anatomical observations indicate that at birth there is often a slight constriction of the duodenum where it is crossed by the mesentery, and it is possible that some such developmental narrowing predisposes to the condition, but although occasionally seen in childhood duodenal ileus usually becomes manifest only in adult life.

The third part of the duodenum is generally the most affected, and it may so dilate as to bulge forwards below the transverse mesocolon. Occasionally the dilatation is most obvious in the first and second parts of the duodenum, which project like a second stomach to the right of the pylorus. The stomach is always large also, but the pylorus may or may not be dilated.

Duodenal ileus is important in itself, as a possible cause of severe bilious attacks, but it is equally important in that it may prejudice the success of operation on other parts of the abdomen. It is no doubt responsible for some instances of pernicious vomiting after gastro-jejunosomy, and it may be responsible for leakage from the duodenal stump after gastrectomy.

DUODENAL DIVERTICULA

Duodenal diverticula are usually regarded as somewhat rare lesions, but according to several anatomical studies it would appear that they are not uncommon. Failure to recognize them is due to the absence of any definite symptomatology, and to the difficulty of portraying them by radiography. Apart from a rare form of pouching which occurs exactly at the duodenal papilla, two types of diverticula may be recognized—the primary type, in which no obvious cause can be discovered, and the secondary type, which results from some local lesion.

Primary diverticula occur usually in the second part of the duodenum, rarely in the third and fourth parts, and never in the first part. They form flask-like protrusions from the concave border of the gut, and are closely related to the vessels entering the duodenal wall. The diverticula are often multiple, and reach their greatest development in middle-aged or old persons. Microscopically, they are found to be composed of the mucous and submucous coats, which have herniated through a gap in the muscularis. The pouches are closely related to the pancreas, and occasionally small islands of aberrant pancreatic tissue are embedded in their walls. They may exert injurious pressure on the common bile duct and the pancreatic duct.

They are usually symptomless and only discovered by chance in the course of radiographic examination of the digestive tract; in some cases, however, vague symptoms of indigestion have been attributed to them. It is remarkable that infection and other complications only supervene with great rarity, owing, no doubt, to the relative sterility

of the duodenal contents. In exceptional cases, stasis in a pouch has predisposed to the formation of concretions.

Secondary diverticula are commonest in relation to peptic ulcer, and consequently occur in the first part of the duodenum. They may arise from the direct traction of an ulcer cicatrix, or from the stretching and "pulsion" of a weakened area of the wall. In either case, they have little clinical import and have no symptomatology apart from that of the causative lesion.

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CHAPTER XXIII

DISEASES OF THE SMALL INTESTINE

ANOMALIES OF INTESTINAL ROTATION

THE mid-gut, which includes the small and large intestine from the level of the duodenal papilla to the neighbourhood of the left colic flexure, undergoes a complicated series of rotations in early foetal life. An understanding of the mechanism of this evolution, and of the derangements to which it is subject, is of considerable importance to the surgeon; for anomalies of rotation may result in errors in the location of the duodenum, the appendix or the cæcum which confound the unwary operator, or they may give rise to secondary pathological changes which it is important to understand.

Mechanism of Normal Rotation. The mechanism of normal rotation has been investigated by several embryologists, and Dott has given an excellent account of it, with, in addition, a valuable description of the various anomalies and their clinical significance. The most complicated evolutions take place before and during the tenth week of intra-uterine life, and before proceeding to describe them it will be necessary to consider the state of the intestinal tract at their inception.

The gastro-intestinal tract consists of three portions, the fore-, mid-, and hind-gut; of these, the fore-gut includes the stomach and the duodenum as far as its papilla, the mid-gut includes from the duodenal papilla to the region of the left colic flexure, and the hind-gut includes the distal colon. In early intra-uterine life each of the three portions is suspended from the dorsal wall of the body cavity by a mesentery, which contains the blood vessel to the three loops, respectively: the celiac artery, the superior mesenteric artery and the inferior mesenteric artery.

The mid-gut at this time consists of a single short loop of intestine, supported by a somewhat fan-shaped mesentery, which is attached to the dorsal wall of the body cavity by a narrow pedicle, the "duodeno-colic isthmus." This isthmus is bounded above and below by the two extremities of the mid-gut (the duodenum and left colic flexure), and these two points lie closely opposed to each other in the mid-line (*see* Fig. 219). Passing ventrally at the isthmus, between the two layers of the mid-gut mesentery, is the superior mesenteric artery, and in its course towards the convexity of the loop it gives off branches to all parts of the mid-gut. The proximal or pre-arterial branches become the vasa intestinales, and the portion of gut they supply becomes the jejunum and ileum; the distal or post-arterial branches become the ileo-colic and right colic arteries, and the distal part of the mid-gut becomes the proximal colon. The importance of this disposition lies in the fact

that a voluminous gut with its mesentery is attached by a very narrow pedicle, upon which it may swing and rotate with ease.

At the fourth week of intra-uterine life the greater part of the mid-gut is extruded from the main abdominal cavity by the rapid increase

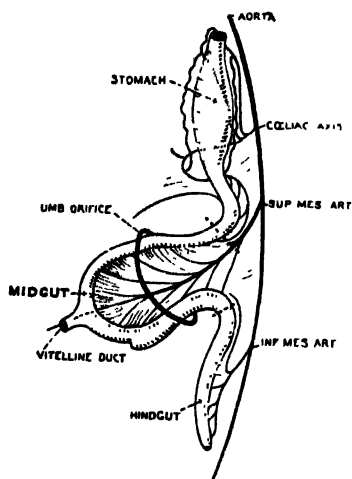


FIG. 219. Intestinal rotation. (1) Before the first stage. (After N. M. Dott.)

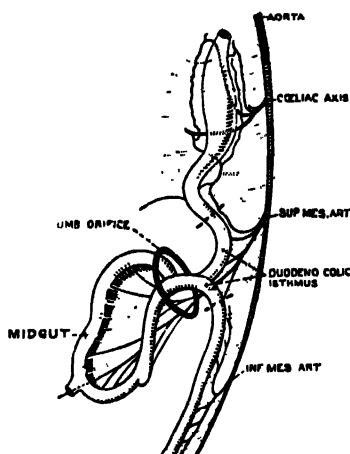


FIG. 220. Intestinal rotation. (2) Completion of first stage (lateral view). (After N. M. Dott.)

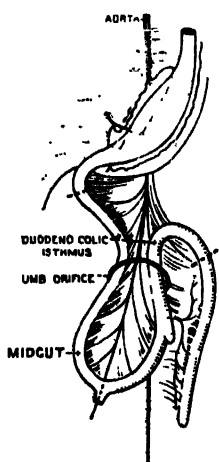


FIG. 221. Intestinal rotation. (3) Completion of first stage (anterior view). (After N. M. Dott.)

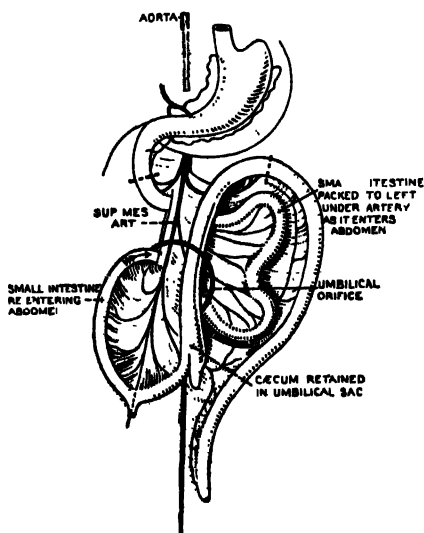


FIG. 222. Intestinal rotation. (4) Second stage in progress. (After N. M. Dott.)

in size of the liver and other organs, and the mid-gut comes to lie within the umbilical cord—a “physiological hernia.” Rarely such a hernia persists (exomphalos). The principal stage of the normal process of rotation occurs when this hernia is reduced, for the re-entering intestines become subject to various mechanical factors inside the abdomen.

The first stage is a simple one, and consists in anti-clockwise rotation of the whole mid-gut loop through 90 degrees. The growing stomach projects its pyloric end towards the right side of the mid-line, and thus carries the proximal end of the mid-gut to the right. The base of the mid-gut loop now lies transversely with the duodenal papilla and the left colic flexure at almost the same level, and the small intestine lies to the right of the mid-line, the proximal colon to the left (*see Fig. 220*).

The second stage includes the crucial phase of the process of rotation. It takes place at the beginning of the tenth week, when the mid-gut returns from the umbilical cord into the general body cavity, and its normal progress depends upon various mechanical influences to which the gut then becomes subjected. Its effect is to rotate the mid-gut loop through a further 180 degrees in the anti-clockwise direction.

The first part of the mid-gut to return to the abdomen is the proximal end, the duodenum and jejunum, which returns in the line of its long axis. The cæcum, owing to its bulk, is the last portion to be reduced, and while it lies in the umbilical cord it exerts an important influence upon the rotation process, for it holds the superior mesenteric artery tautly forwards and this provides an axis around which the small intestine may rotate.

When the re-entering coils of duodenum and jejunum (at present lying to right of the mid-line) reach the abdomen, they meet the resistance of the liver, and they are deflected downwards on the right side. With further deflection in the same (anti-clockwise) direction they become propelled behind the taut axis of the superior mesenteric artery, and thus the uppermost coil, the terminal duodenum, comes to lie transversely below and behind this vessel. The jejunum and ileum follow the same course, and when eventually the cæcum returns to the abdomen the whole small intestine lies on the left side, and the proximal colon is displaced to the right (*see Figs. 222 and 223*).

The third stage, which is a less complicated one, concerns the descent of the cæcum and proximal colon to their adult position, and the subsequent fixation of the intestinal mass.

At the conclusion of the second stage the cæcum, which has just been returned to the abdominal cavity, lies immediately deep to the umbilicus. By various mechanical influences that need not be discussed the cæcum is propelled upwards and to the right to reach the subhepatic region, and from this point it travels downwards to reach its adult position in the right iliac fossa.

Up to this point the whole mid-gut remains suspended in its fan-shaped mesentery from the duodeno-colic isthmus, but now certain parts of it become fixed to the dorsal abdominal wall. That part of the mesentery which encloses the superior mesenteric artery becomes adherent to the dorsal wall along an oblique line extending towards the right iliac fossa, and this line subsequently is known as the *root of the mesentery*. In this process the duodenum becomes fixed where it passes beneath the artery, and it thus acquires its retroperitoneal position. Lastly the post-arterial mesentery, containing the right colic and ileo-colic vessels, fuses with the posterior parietes, and the proximal colon thus becomes fixed.

Derangements of Rotation. Derangements of the first stage are very rare, while those of the third stage are so frequent as to be commonplace. The most interesting though rare anomalies are those of the second stage. These have been classified by Dott in three principal groups as follows :—

(1) *Non-rotation.* Here the gut as it enters the abdomen fails to rotate, and the small intestine remains on the right, the proximal colon on the left. The duodenum does not pass horizontally across the abdomen, but passes directly downwards, and the coils of jejunum lie close below the liver. The lower part of the ileum crosses the midline

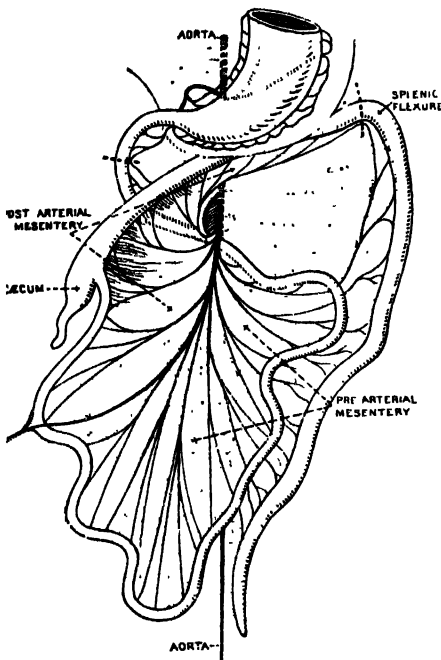


FIG. 223. Intestinal rotation. (5) Second stage completed. (After N. M. Dott.)

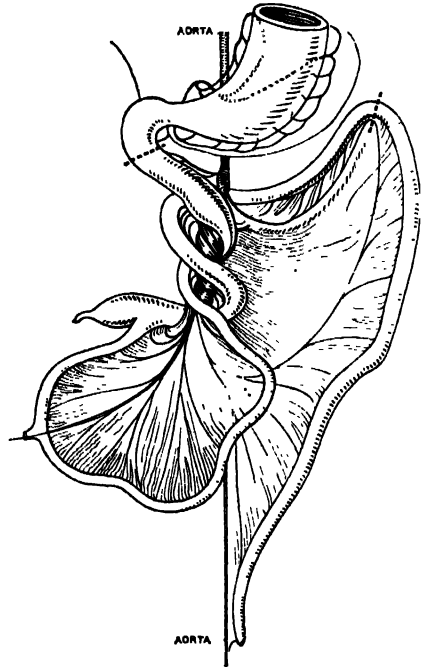


FIG. 224. Anomaly of intestinal rotation. Volvulus neonatorum. (After N. M. Dott.)

and enters the right side of the cæcum. The ascending colon lies to the left of the midline, and the transverse colon, which is short, is related to the left part of the greater curvature of the stomach.

The anomaly of non-rotation is of great practical importance, for as a result of it the cæcum and appendix are displaced and in diseases such as appendicitis the symptoms are left-sided. The anomaly is also important for its secondary effects, for the gut sometimes remains unfixated and unduly mobile. If the whole mid-gut remains free, suspended from its narrow duodeno-colic isthmus, it is very apt to undergo volvulus in the early days of life—*volvulus neonatorum* (see Fig. 224). This is a condition of great gravity. It differs from volvulus in adults in several particulars which may render its recognition, even at the time of operation, a matter of some difficulty. The whole mid-gut

is affected, but since its lower end is less acutely twisted than its upper end, the gut remains collapsed, and the clinical features are those of duodenal obstruction, with little distension in the lower abdomen. Moreover, since the blood supply is little affected the deep discoloration so characteristic of other forms of volvulus may be lacking. The condition should be suspected when a young infant, previously in good health, suddenly commences to vomit bile-stained material.

(2) *Reversed Rotation.* This is an interesting anomaly, which is believed to be due to the return of the proximal colon to the abdominal cavity *before* the jejunum. The proximal colon therefore is the first part to rotate, but in the reverse (clockwise) direction, and it comes to lie in the position normally occupied by the duodenum, often in a tunnel deep to the root of the mesentery of the small intestine. In spite of the altered rotation, however, the remainder of the gut eventually reaches the normal adult position. Clinically it is of importance, for the transverse colon may be constricted as it lies deep to the mesentery, and obstruction may result.

(3) *Malrotation.* This includes several irregular and less clearly understood defects of rotation, whereby part or the whole of the mid-gut may be displaced.

Derangements of the Third Stage. The commonest of these concern the descent of the cæcum and proximal colon, and their subsequent fixation. Failure of descent leads to fixation of the cæcum in the loin or close under the liver; and too prolonged descent, with lack of fixation, leads to all degrees of mobility of the cæcum and proximal colon. The appendix may remain high up in the loin in the retrocolic and retrocæcal positions, and its tip may extend as far as the liver. When the proximal colon remains unfixed and floating it may undergo volvulus in adult life.

ANOMALIES OF THE VITELLINE DUCT: MECKEL'S DIVERTICULUM

The vitelline duct or yolk stalk forms a communicating channel which in early embryonic life passes from the yolk sac along the umbilical cord to the intestinal canal. In normal circumstances it becomes obliterated at about the sixth or seventh week of intra-uterine life, but it may persist to a greater or less extent and may cause trouble at a later date. The obliterative process begins at the umbilicus and extends to the intestine, and consequently the intestinal end of the duct persists most frequently. The common form is a small blind diverticulum projecting from the ileum a few feet above the ileocæcal sphincter. The diverticulum may be finger-like or rounded. It is usually two or three inches long, and projects from the antimesenteric border of the gut, with its end free in the peritoneal cavity. Occasionally it arises on the mesenteric aspect and lies enclosed in the ileal mesentery. In its customary intraperitoneal situation it may terminate abruptly, with a rounded or conical end, or it may taper into a thin fibrous cord, attached by its other end to the mesentery. This cord represents the obliterated vitello-intestinal artery. To it the

diverticulum owes much of its potential danger, for the cord may snare portions of intestine and so cause obstruction. Rarely a remnant of the vitelline vascular system may persist although the vitelline duct is completely obliterated. Thus a fibrous cord representing the vitelline artery may pass from the umbilicus to the ileal mesentery, whilst the vitelline vein may be represented by a cord extending from the umbilicus towards the third part of the duodenum.

The vitelline duct may remain patent through its whole length. Occasionally only the umbilical end remains patent, forming a small sinus, which discharges at the umbilicus, and it may prolapse on to the anterior abdominal wall (the so-called enteroteratoma). An intermediate portion may persist and form a freely mobile cystic swelling in the peritoneal cavity—entero-cystoma. Rarely a portion abnormally placed in the mesentery may form an “enterogenous” type of mesenteric cyst (*see p. 549*).

In some cases stenosis of the ileum may coexist, ranging from slight narrowing to complete obliteration. Sometimes there is a diaphragm of mucous membrane perforated by a mere slit. This may allow the passage of intestinal contents, but solid objects such as fruit stones are liable to become impacted.

Complications. The complications of a persisting portion of the vitelline duct are legion, and there must be few surgeons who have had no experience of the remarkable intra-abdominal entanglements to which it may give rise. For convenience they may be classified as (1) intrinsic complications, primarily affecting the diverticulum itself, and (2) extrinsic complications, affecting other portions of the intestine.

(1) *Intrinsic Complications.* Not uncommonly the communication between the diverticulum and the intestine is a small one, and it may undergo progressive stenosis until completely occluded, so that the diverticulum dilates to form a cyst, which fills with mucoid material, and may reach great size. Infection of the diverticulum may occur, and closely simulate appendicitis, for which it is liable to be mistaken. In exceptional cases an ulcer may form in the diverticulum and may give rise to hæmorrhage into the bowel, or may perforate into the peritoneal cavity. The diverticular wall may contain traces of heterotopic gastric mucous membrane, and the ulcer may thus be regarded as of peptic origin. Not infrequently simple tumours, such as adenoma or myoma, arise in the wall of a diverticulum.

(2) *Extrinsic Complications.* These arise most commonly from the action of the whip-like fibrous cord attached to the apex of the diverticulum. The cord may be free at first, but it is apt to contract adventitious adhesions, and thus to provide a snare through which a hernia may occur. A diverticulum fixed to the umbilicus provides a fulcrum for volvulus of the intestine. Even if unfixed a dilated diverticulum may by its weight achieve the same result. Lastly, and very rarely, a diverticulum may prolapse inside the ileum and lead to enteric intussusception.

Multiple Diverticula of the Small Intestine. Multiple diverticula occur, though rarely, in the jejunum or the ileum, the latter situation

being the more common. They may be present in large numbers, affecting several feet of the gut. Unlike diverticula of the colon, they project on the mesenteric aspect of the bowel, along the line of the blood vessels. They consist of mucous and submucous tissue alone, protruding through gaps in the muscular tunic. It is generally assumed that they are developmental in origin, though the suggestion has been made that they are pulsion diverticula, arising from irregular peristaltic contractions and consequent increase in the pressure within the gut. Clinically they are not important, for infection and other complications are extremely rare.

INTESTINAL OBSTRUCTION

From a pathological standpoint there are four chief types of intestinal obstruction: (1) Simple obstruction, produced either from conditions within the bowel or from without; (2) obstruction, complicated by interruption of the blood supply of the affected portion of intestine (strangulation); (3) obstruction at two, usually adjacent, points in the intestine (closed-loop obstruction); and (4) adynamic or paralytic ileus. Obstruction may be acute, subacute, or chronic, and chronic obstruction may become acute.

Simple Obstruction. Simple obstruction may occur alone, and always is a basic feature of other varieties. As it is the least complicated type it has formed the model for the study of the general phenomena of obstruction. Except in adynamic ileus, intestinal obstruction is mechanical in origin, and there are many well recognized ways in which it may be brought about, but often the mechanism takes unusual forms. Simple obstruction may result from developmental errors, from impaction of a foreign body, or from narrowing of the bowel by a fibrous or a carcinomatous stricture. As the contents of the small intestine are fluid, stenosis may reach an extreme degree before obstruction results. Simple obstruction, especially in the small intestine, occurs frequently as a result of angulation or constriction by a fibrous band or by an adhesion such as may result from peritonitis or an abdominal operation.

Strangulation. In this variety of obstruction not only is there closure of the lumen of the bowel, but the blood vessels of the segment implicated are also occluded, so that the vitality of the bowel is endangered. The veins only may be affected (as is usual), or the arteries and veins simultaneously. Strangulation is always more serious than simple obstruction because primary shock may be very severe and toxæmia or peritonitis may determine an early fatal issue. Death may occur very rapidly, and often without the customary features of simple obstruction. Strangulation may occur in the small or the large intestine and the commonest causes are intussusception, volvulus, strangulated hernia, and mesenteric vascular occlusion (*q.v.*).

Closed-loop Obstruction. This type of obstruction is not often observed in an uncomplicated form. It may occur when a loop of intestine becomes obstructed at the neck of a hernial sac, and when a fibrous band ensnares a loop of intestine. The changes to be expected

in the intestine in this variety of obstruction are comparable to those which develop in the obstructive types of appendicitis and are governed by the infectivity of the bowel contents and the completeness of the obstruction.

Adynamic or Paralytic Ileus. The designation adynamic ileus is reserved for those not uncommon cases in which intestinal propulsion fails on account of nervous influences, and those in which there is no obvious mechanical factor. It is observed most often after comparatively simple operations on the abdominal viscera, in which there may have been little or no interference with the intestine. It may follow operations which do not open the peritoneal cavity, *e.g.*, nephrectomy.

Adynamic ileus is often an important cause of abdominal distension in general peritonitis. It is a common complication of fracture of the spine.

There may be all degrees of severity between temporary abdominal distension and obstruction indistinguishable from that of mechanical origin. The underlying causes of the derangement of peristalsis are not fully understood; there are probably many contributory factors, such as depression of muscular and nervous activity, interference with the absorption of intestinal gases, vasomotor disturbances of the mesenteric vessels and increase of intra-abdominal pressure. In the later stages overstretching of the muscle coats of the bowel is an important factor in annulling peristalsis.

Local Effects of Obstruction

The local effects of obstruction depend upon its cause, its acuteness, and its level in the intestinal tract. The outstanding feature is engorgement of the splanchnic vessels, which usually results in a clear or a slightly blood-stained effusion into the peritoneal cavity; definite extravasation of blood occurs when strangulation is present. The intestine is much dilated proximal to the obstruction, and its wall is dusky red or cyanotic and may finally show patches of gangrene, even in the absence of strangulation. The mucous membrane is deeply congested and may be ulcerated. Distal to the obstruction the intestine is collapsed and empty and may be in a state of spasm. When obstruction has persisted for some time the lumen of the intestine contains a large quantity of yellowish-brown fluid of high bacterial content and of faecal odour. When the obstruction is low down in the small intestine the stomach, duodenum, and jejunum contain the greatest quantity of fluid, and the intermediate part of the intestine contains less fluid and more gas, whereas the intestine immediately proximal to the obstruction may contain only gas. The fluid in the obstructed intestine is composed mainly of gastric secretion, bile and pancreatic juice, and the secretion of the intestine itself. Absorption of readily diffusible substances is almost at a standstill within the obstructed bowel.

General Effects of Obstruction

Vomiting is one of the commonest effects. It comes on early and is more copious when the obstruction is high up in the small intestine, whereas when the obstruction is low in the small intestine or in the colon

it is a late feature or may not occur at all. In the early stages the vomit is clear and consists of gastric contents, later it contains bile, and in the advanced stages it is brown and offensive from putrefactive changes. For some time before death free hydrochloric acid is absent, although the total chloride content of the stomach is normal. The vomiting contributes chiefly to the dehydration which is so constant a feature of intestinal obstruction, and, in addition, it is responsible for the loss of hydrochloric acid and sodium chloride which finally leads to depletion of the body chlorides. Dehydration may reach such a degree that at least 6% of body weight in water alone is lost. Dehydration leads to dryness of the skin, increasing thirst, and diminished urine output. The blood becomes increasingly concentrated so that the erythrocyte count rises; and the sedimentation rate is prolonged and the total blood volume much reduced.

Obstruction is sooner or later associated with very severe constitutional disturbance and sometimes toxæmia: this may be manifest by pallor and slight cyanosis, a rapid pulse rate, and a low blood pressure. It is rather paradoxical that the higher the obstruction is situated in the intestine the greater is the toxæmia and the more lethal are its effects. Obstruction in the jejunum may be fatal in two days, whereas obstruction of the colon may be tolerated for as many weeks.

In obstruction there are definite and constant chemical changes in the urine and in the blood. They develop more rapidly and are more pronounced in high obstruction, and may be only slight in obstruction low down. These changes are of great importance because they afford an index of the degree of depletion, and they suggest the lines upon which the constitutional effects of the obstruction may be combated. These changes are often slight or absent in strangulation.

Changes in the Urine. The urine becomes scanty, owing to loss of body fluids by vomiting. The scantiness leads to a greatly increased concentration of urea in the urine—it may be four or five times the normal. The excretion of urea is increased, but probably to no greater extent than is accounted for by starvation, and it is not due to any disturbance of renal function. The excretion of chlorides is greatly diminished, and in the later stages they disappear.

Changes in the Blood. The most important changes are those of the blood chlorides and potassium, the carbon dioxide combining-power, and the non-protein nitrogen and blood urea. The higher the obstruction the more profoundly and rapidly they are affected.

The blood chlorides become gradually reduced from the normal of 500 milligrams per cent. to as low as 350 milligrams per cent. At about that level they disappear from the urine, and their disappearance is an indication of a dangerous degree of toxæmia. The carbon dioxide combining-power of the blood, which is an accurate indication of the alkali reserve of the body, may increase from the normal of 53 to 78 volumes per cent. to a hundred or over. The alkalmia is a result mainly of chloride loss, because the continued loss of chlorine ions is accompanied by retention of sodium ions which, in an attempt at maintaining the electrolytic content of the blood, combine with carbon-dioxide.

The blood potassium, which is the basic salt of intracellular fluid, is reduced mainly from the loss by vomiting.

The rise in non-protein nitrogen and blood urea is due to dehydration, starvation and increased cellular breakdown.

The Cause of Toxæmia and Death in Simple Obstruction

No problem in surgical pathology has stimulated more clinical and experimental research than that concerning the causes of toxæmia and death in intestinal obstruction.

It is now certain that the lethal factors differ according as the obstruction is high up in the intestine or low down.

In high obstruction, such as occurs in post-gastro-enterostomy vomiting, acute dilatation of the stomach and duodenal ileus, dehydration and profound biochemical changes affecting the chlorides and sodium of the blood and tissues afford sufficient explanation of the rapidly fatal effects, and at once suggest the lines upon which treatment should be conducted in order to correct the depletion.¹

In obstruction low down in the ileum, which is the common clinical form, the pathological features are not susceptible of such simple explanation. The biochemical changes are slight even though obstruction may have persisted for a considerable time, yet there is obvious toxæmia. Therefore, it is not surprising that absorption of a toxin from the bowel contents, its wall, or both, has been held responsible.

The nature of the toxin and its mode of production remain obscure. Earlier investigators suggested that a proteose elaborated in the intestinal wall was responsible; others that a bacterial toxin of split protein or *Cl. Welchii* origin might explain the phenomenon.

Recent experimental workers such as Aird, Knight and Slome have brought forward strong evidence that a diffusible toxin, probably of the nature of histamin, is an important underlying factor in the toxæmia. Aird's experiments suggest that the sustained intra-intestinal pressure present in obstruction arrests the circulation and retards absorption. The state of tissue anoxæmia favours the development of depressor substances, which on release of the obstruction may, with resumption of normal absorption, exercise a profound; even fatal, effect on the circulation. This observation is in keeping with the well-known observation that death often occurs suddenly after relief of severe obstruction; it suggests the advisability of gradual decompression of distended bowel to avert an overwhelming depressor effect on the circulation.

Special Features of Strangulation. Clinical and experimental investigations suggest that the cause of death in venous strangulation within the peritoneal cavity depends directly on the length of bowel

¹ The daily intake of water in health to maintain a correct balance is 1,750 to 3,200 c.c. It is estimated that in intestinal obstruction, in which very large quantities are lost, at least 3,500 c.c. of water are required daily in addition to the normal intake.

To maintain a normal sodium chloride level in the blood and tissues the intake requires to be about 6 gm. daily. To correct severe hypochloremia 15 to 20 gm. of sodium chloride are required daily for every 100 mg. that the plasma chloride is depleted.

involved. When long loops are involved death is due not to toxæmia but to circulatory collapse as a result of rapid loss of blood plasma by the withdrawal of a large quantity of blood from the circulation, an effect equivalent to an internal hæmorrhage. In such circumstances, death from shock may occur so quickly that dehydration and hypochloræmia do not develop. When moderate-sized loops are strangulated, shock and blood loss are less prominent and death occurs much later from the absorption of a toxic peritoneal exudate elaborated by proteolytic organisms in the tissues of the intestinal wall. In strangulation within a hernial sac only a small surface is available for absorption of toxins, and in such cases death is due to the obstruction which accompanies the strangulation. When strangulation affects arteries and veins simultaneously death occurs from a combination of toxæmia and peritonitis resulting from the action of intestinal bacteria on, and their permeation of, the bowel wall.

A practical conclusion from the above observations is that strangulation within the peritoneal cavity is a most urgent form of obstruction. When a large segment of intestine is implicated the shock resulting from withdrawal of blood from the circulation should be counteracted by transfusion. In cases of strangulation affecting shorter loops further absorption of toxin should be averted by evacuation of the fluid exudate, gentle handling of the devitalised bowel and its prompt exteriorisation. In no circumstances should a bowel of doubtful viability be returned to the peritoneal cavity.

INTUSSUSCEPTION

(Intussusception is the invagination of one part of the intestine into the part immediately adjoining.) It may occur at any age, but is commonest in healthy males during the first year of life. It is the most frequent cause of intestinal obstruction during early life. With few exceptions, the invagination of the bowel is from above downwards; and usually the terminal portion of the ileum is the part primarily affected.

Ætiology. In the majority of cases there is no obvious anatomical explanation, and there is considerable evidence that the underlying cause is derangement of the normal peristaltic mechanism of the intestine, excited by errors in diet. Probably faulty diet is an exciting factor, for intussusception is especially prevalent in children of the poor, and has its greatest incidence between the fourth and seventh months of infancy, when injudicious additions to the child's dietary are often made.

It has been suggested that in many cases there is an inherent defect in the neuromuscular coordination of the intestine, such as would allow a localized constriction, once formed, to persist unduly, and favour invagination into a passive segment of bowel immediately beyond. (In infancy, the inhibitory nervous apparatus is developed latest, and it is apt to lag behind the motor, so that at an early age the inhibitory activities of the parasympathetic nerves are functionally weak, and the tonicity of plain muscle outweighs for a time its capability of relaxation.) Such inherent nervous disabilities in the gut may account for the frequency of intussusception in vigorous male

babies with strong musculature as compared with puny children, with atonic intestines, for its tendency to recur in some cases, and for the rarity of the disease in adults. The neurogenic explanation is supported by the observation that intussusception may occur spontaneously in animals after paralysis of the intramural nerve plexus of the gut.



FIG. 225. Acute intussusception of ileocaecal region.

(Department of Surgery, University of Edinburgh.)

three layers of intestine—entering, returning, and receiving; and on cross-section these appear as three concentric tubes. The outer or receiving layer is known as the sheath or *intussusciens*, the entering and returning layers as the *intussusceptum*; the most advanced part of the intussusceptum, where the entering and returning layers become continuous, is known as the *apex*; the ring where the returning layer becomes continuous with the sheath is known as the *neck*. The entering and returning layers have their serous surfaces opposed, but usually they are partly separated by that portion of the mesentery which is drawn in as the intussusception proceeds.

Method of Progression. The apex of an intussusceptum is formed of the same segment of intestine from first to last. That segment is the starting point; it speedily becomes congested and swollen, and consti-

Structural peculiarities of the intestine also may favour the development of intussusception. Thus intussusceptions of the ileocaecal region are specially apt to develop if the ascending colon is unusually mobile owing to the abnormal presence of a mesocolon; and also lymphoid tissue is relatively excessive in that region, and readily becomes swollen and congested.

In older children and in adults intussusception is generally initiated by some local lesion such as a polypus, a diverticulum, or an inflamed lymphoid patch. In adults it may begin at the site of a malignant growth, and is then probably brought on by the peristaltic effort of the intestine to pass the obstruction.

Anatomy of an Intussusception. As one part of the intestine passes inside another, the resulting intussusception is composed of

tutes a partial obstruction. The peristalsis behind it, striving to overcome the obstruction, drives it onwards as though it were a foreign body into the part of the intestine beyond, invaginating that part. The congestion and œdema make this apical segment so stiff that the inner tube cannot roll round and become part of the middle or returning layer, and therefore, as the invagination proceeds, the middle layer is increased wholly at the expense of the outer layer or sheath. The process of indrawing of the sheath and consequent elongation of the returning layer is unretarded until tension is put upon the mesentery, and after that, onward movement occurs by the stretching, torsion, or angulation of the mesentery at the neck of the intussusception. It is probable that the intermittent spasmodic pain characteristic of this disease is due to that traction. On account of the tension exerted through the mesentery the intussusception alters its position and becomes curved with its concavity towards the root of the mesentery. In cases where the invagination of the bowel is very great, as when an ileocæcal intussusception reaches the rectum, the bowel frequently forms the arc of a circle, the centre of which is at the root of the mesentery, and the increase in length of the intussusception is gained by the spiral torsion of the mesenteries.

On account of the dragging effect of the mesentery, the apex of an intussusception may become tilted and its orifice oblique or eccentric, and the free antimesenteric border of the returning part may then slip down for an inch or two beyond the true apex. This phenomenon is most often observed in intussusception of the ileocæcal region and, in such cases, when reduction is brought about the colic valve will appear before the cæcum, which is found to be "dimpled" on its serous aspect from being dragged down in advance of the apex.

Pathological Effects of Intussusception. The most important pathological effects of intussusception are due to occlusion of the blood vessels in the mesentery of the affected part of the intestine, and intussusception is virtually intestinal obstruction with the risk of strangulation (*q.v.*).

The first effects are congestion and œdema from the impeded venous return; they are followed by the discharge of blood-stained mucus into the bowel; and long continued venous stagnation leads to thrombosis. The œdema is most marked at the apex and in the returning layer; the apex becomes swollen and knob-shaped and may form an obstacle to reduction. Finally pressure is sufficient to occlude the arteries and then necrosis and gangrene of the invaginated bowel ensue. The vitality of the sheath is seldom imperilled. As a result of necrosis, perforation of the bowel may occur. In rare cases after gangrene has set in, the necrosed intussusceptum may be extruded from the bowel as a slough, resulting in spontaneous cure.

The rapidity of these changes varies, and, therefore, acute, subacute, and chronic types of intussusception are recognized.

Special Types of Intussusception

(a) **Ileocolic** is the commonest variety of intussusception, especially in infants. The invagination usually begins in the last few inches of

the ileum and the apex passes through the ileocæcal orifice. As the intussusception increases at the expense of the colon the ileocæcal valve and the appendix become invaginated—iliaco-ileocolic type.

(b) **Enteric intussusceptions**, originating in the small intestine, are rare in infants, but may occur in adults as a result of the presence of a tumour.

(c) **Double intussusceptions** are those in which the sheath has become folded upon itself. They are almost invariably found in intussusceptions beginning at the lower end of the ileum or at the ileocæcal valve. Triple intussusception also may occur.

(d) **Retrograde intussusceptions** are those in which the lower part of the bowel is invaginated into the part above. They have been most often found in the jejunum and in the transverse and descending colon. Sometimes they have been observed at post-mortem following a blow on the abdomen. The intussusception may be multiple. Several cases of retrograde intussusception of the jejunum into the stomach through the orifice of a gastro-jejunostomy have been reported (*see p. 467*).

(e) **Chronic intussusception** may occur as a primary condition in infants and in adults. It is usually of an ileocolic type. The intussusception may persist for months or even years. Adhesions may form between the invaginated coils of intestine and render it irreducible, but often there are no adhesions. Ulceration of the implicated coils of intestine is common and the sheath may become perforated at several points. Chronic intussusception gives rise to paroxysms of intestinal colic attended by tenesmus and mucoid discharge from the colon. It may culminate in acute obstruction.

(f) **Intussusception of the appendix** is very rare. The invagination may begin at any point in the appendix, or partial or complete inversion of the appendix into the cæcum may occur followed sometimes by colonic intussusception. In some of the reported cases, pathological conditions of the appendix, such as new growths, mucocele and concretions, have been responsible.

TUBERCULOSIS OF THE SMALL INTESTINE

Tuberculosis of the small intestine is not uncommon. It affects especially adolescents and young adults, and often it is accompanied by tuberculous lesions in the cæcum and in the mesenteric lymph glands.

The disease is most common in the subjects of pulmonary tuberculosis, and is then attributable to infection by swallowed sputum. It is usually a grave complication. Sometimes there is no obvious affection of the lungs, and in such cases a milk-borne infection may be responsible.

The distal part of the ileum is affected most often, for this is the most actively absorptive part of the gut, and, in addition, is the part most richly supplied with lymphoid tissue. The disease arises first in the Peyer's patches and spreads thence to the neighbouring parts of the intestinal wall, forming ulcers of typical tuberculous characters, with pale granulating bases and undermined edges. The ulcers extend in the direction of the lymph drainage and consequently they become

elongated and lie at right angles to the long axis of the gut. Sloughing is much less in evidence than in typhoid ulcers.

Tuberculous ulcers of the intestine rarely perforate, and their chief surgical importance lies in the fact that in healing by fibrosis they tend to constrict the lumen of the gut and to give rise to strictures. Such strictures may be single, but often are multiple. Since the intestinal content is fluid they give rise to no symptoms during a long period, but eventually they tend to cause chronic and finally acute obstruction. Obstruction may be precipitated by the impaction of a foreign body such as a fruit stone, a gall-stone, or inspissated fæces.

Not infrequently in its acute phases a tuberculous ulcer of the intestine may lead to infection of the peritoneum and to the formation of peritoneal adhesions, and these subsequently may give rise to symptoms by exerting traction upon the intestine or by causing obstruction.

ULCERS OF THE SMALL INTESTINE

Apart from peptic ulcers of the duodenum and tuberculous ulcers of the ileum, ulceration of the small intestine is somewhat uncommon. In the majority of cases it is attributable to some definite predisposing condition, and in this category come jejunal ulcers after gastro-jejunosomy, dysenteric and typhoid ulcers, malignant ulcers, and, rarely, stercoral ulcers in the intestine proximal to an obstruction.

There remains a rare but interesting type of ulcer, the so-called *simple ulcer of the small intestine*. This is a shallow erosion, which affects especially the ileum and generally appears to arise in one of the Peyer's patches. It appears to have an especial tendency to perforate acutely, when it gives rise to fulminating and often fatal peritonitis. The cause of such ulcers is not known. In some cases microscopic examination gives evidence of heterotopic gastric mucous membrane in the small intestine, and it is possible that the ulcers may be due to such an anomaly and be thus comparable to peptic ulcers of the stomach or the duodenum. In other cases the ileum contains fæcal masses that have regurgitated through an incompetent ileocæcal sphincter, and the ulcer may be attributable to the abrasion and infection thus induced. In others, again, the ulcer may result from regional ileitis (*see below*).

REGIONAL ILEITIS

This is a non-specific inflammatory process involving a limited segment—from a few inches to a few feet in length—of the intestinal tract. It would appear that the disease has become commoner during the last decade. In the majority of cases it affects the terminal part of the ileum, sometimes encroaching upon the ileocæcal valve and cæcum. Less often it affects a segment higher in the small intestine or in the colon.

At first there is a subacute inflammatory reaction in the wall of the affected part, which becomes swollen with œdema and very congested. The inflammation progresses to ulceration of the mucosa and subsequently to fibrosis with formation of multiple strictures. In severe

DISEASES OF THE SMALL INTESTINE

cases the ulcers penetrate deeply into the intestinal wall, and they may perforate, giving rise to a fulminating form of diffuse peritonitis. More often the inflamed part is walled in by adhesions of omentum and adjacent intestinal coils, so that when the ulcer perforates a localized abscess results. Such an abscess is very apt to spread to the surface and burst, giving rise to a faecal fistula—a complication which is especially apt to occur after an exploratory operation.

The naked eye appearance is characteristic. In the florid, active stage the affected loop of intestine is swollen, soft and spongy with oedema, and is greatly congested. The adjacent mesentery also is oedematous, and contains numerous enlarged glands of soft fleshy consistency. When the intestine is opened, its mucous membrane is seen to be swollen and inflamed, its villi and folds submerged in the general oedema. Multiple irregular ulcers are generally present, and the intervening mucous membrane may present swollen tags like inflamed polypi.

In the later stages the congestion and oedema are less marked, and the segment becomes tough and fibrous, with multiple strictures. At this stage it closely resembles the hyperplastic form of ileocaecal tuberculosis.

Microscopic examination reveals various degrees of acute and sub-acute chronic inflammatory change, non-specific in character. There is an infiltration of inflammatory cells, and according to the stage of the process polymorph leucocytes, lymphocytes or plasma cells may predominate. In the chronic phase foreign-body giant cells may occur. They are liable to be mistaken for tubercle giant cells.

The cause of regional ileitis is not fully understood. It has been attributed variously to streptococci, coliform and dysenteric organisms, and more recently to sarcoidosis. At present proof of a specific infecting agent is lacking.

TUMOURS OF THE SMALL INTESTINE

The small intestine is an uncommon site for tumours. Simple papillary adenoma, either single or multiple, may grow from the mucous membrane and form polypoidal lobulated growths. Leiomyomata are often multiple. They form rounded, pedunculated



FIG. 226. Carcinoma of the jejunum. The tumour is of scirrhus nature, and forms a small, pale, hard mass, which has encircled the gut and has given rise to a very narrow stricture.

(Department of Surgery, University of Edinburgh.)

tumours which project into the lumen of the gut. They may undergo malignant change, and give rise to leiomyosarcoma. Fibroma, lipoma and lymphoma and argentophil tumours may occur. The special importance of simple tumours of the small intestine is that they frequently give rise to intussusception. Indeed, the vast majority of intussusceptions occurring after infancy are due to this cause. Of malignant tumours, an adeno-carcinoma is the most common. It occurs in the ileum more frequently than in the jejunum and forms a small white scirrhus growth which tends to encircle the gut, and may form a complete ring stricture. Since the intestinal content is fluid, symptoms of obstruction develop only at a late stage. Sarcoma also may occur in the small intestine either as a primary growth, generally a lympho-sarcoma, or as a myosarcoma developing in a simple muscle tumour. Sarcoma tends to form a more massive growth, and since it does not constrict the bowel it is less likely to give rise to obstruction.

Argentaffine Tumours of the Small Intestine. This type of tumour resembles the carcinoid tumour of the appendix and is most common in the terminal portion of the ileum where it is often responsible for obstruction. It has occurred in a diverticulum. An argentaffine tumour resembles a carcinoma in that it invades the tissues locally and may extend into the regional lymph glands. The tumour is yellow in colour and of firm consistency without any tendency to necrosis. Experience has proved that removal of the tumour and of invaded lymph glands gives permanent immunity to recurrence, unless, as rarely, the liver is involved.

ENTERIC PNEUMATOSIS (Gas Cysts of the Intestine)

This rare condition is characterized by the development of multiple gas-containing cysts in the subserous coats of the intestine. The cysts lie principally in relation to the ileum, but not uncommonly they extend over the whole length of the small intestine or even over the cæcum and ascending colon. They are arranged in clusters and are usually situated on the mesenteric aspect of the gut. They rarely exceed the size of a pigeon's egg. At first the cysts are sessile, but later they may become pedunculated and hang free in the peritoneal cavity.

The cyst wall is often thin and translucent, and is then composed of delicate connective tissue lined by endothelium. Sometimes the wall is thickened, and is infiltrated by lymphocytes, mononuclear cells, and giant cells of the foreign body type. The gas, which is under pressure, is composed principally of nitrogen, with smaller proportions of oxygen and carbon dioxide and occasionally other gases.

Gas cysts are rare in man, and are usually found by chance on exploration of the abdomen for gastric or duodenal ulcer or, less often, other diseases. Occasionally cysts of similar nature occur in the vaginal wall in pregnancy.

Enteric pneumatosis gives rise to no symptoms, and is of no clinical importance, but its puzzling ætiology has attracted much attention, and several ingenious theories have been advanced. It has been

suggested that the gas is a product of aerogenic organisms, but this is not supported by bacteriological evidence. Many authors have suggested that the origin of the cysts is mechanical, and that gas of intestinal origin is forced through minute fissures in the mucous membrane as a result of vomiting, or irregular peristaltic action, but against this view is the absence of intestinal flora within the cysts.

Masson in a valuable paper has supported the view of a chemical origin. He affirms that the cysts are dilated lymph or chyliferous channels, and that the gas is derived from chyle by chemical interaction with acid products of intestinal fermentation. In support of this view



FIG. 227. Cystic pneumatosis (gas cysts of the intestine). Numerous air-containing cysts, some sessile, others pedunculated, lie under the peritoneum on the surface of the small intestine.

(Department of Surgery, University of Edinburgh).

he points out, firstly, that chyle contains large quantities of carbon dioxide in the form of alkaline carbonates, and, secondly, that gas cysts occur most often in conditions associated with increased intestinal acidity. Presumably carbon dioxide set free in this manner is subsequently replaced by nitrogen diffused from the blood, just as oxygen introduced into the pleural cavity may be replaced.

It is interesting to observe that enteric pneumatosis is common in swine fed on dairy refuse, and it is thought that the large quantities of lactic acid thus consumed provide the acid necessary for the gas production.

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CHAPTER XXIV

DISEASES OF THE COLON

CONGENITAL ABNORMALITIES OF THE COLON

Congenital Microcolon

In this rare condition the entire colon with the exception of the rectum is extremely small, and its lumen may scarcely admit a quill. Though reduced in calibre its anatomical structure is perfect ; it is a colon in miniature. The ileocaecal valve is normal in appearance but the small intestine is hypertrophied and contains putty-like masses of meconium. Other congenital abnormalities, such as atresia or absence of a segment of intestine, may coexist.

Although many theories have been advanced, the origin of congenital microcolon, like that of other developmental errors of the intestines, is not understood. The condition results in acute obstruction soon after birth. Ileostomy offers the only means of relief, but in the early days of life leads to progressive dehydration which is not survived.

Congenital Megacolon (Hirschsprung's Disease)

The outstanding feature of this disease is that the colon, which is dilated and hypertrophied, is from birth or soon afterwards unable to evacuate its contents in a normal fashion, although there is no organic obstruction of its lumen. Male children are affected more often than females in the proportion of five to one.

Morbid Anatomy. The dilatation of the colon is usually most extreme in the sigmoid portion and in about 87% of cases is confined to that part. In 34% of cases the upper part or the entire rectum¹ is also affected. In others the dilatation may extend to the descending or transverse part of the colon, and in about 25% it reaches the ileocaecal valve. The small intestine, however, is never affected. Cases have been observed in which only the proximal parts of the colon (ascending and transverse colon) have been affected. In many cases, at least 10%, there is an associated dilatation of the bladder. In exaggerated cases the dilated colon may have a diameter of 15 centimetres or more. In addition to dilatation, the affected part of the colon shows great hypertrophy of its walls, chiefly of the circular muscle : the taeniae are less evident than normally. The serous coat also is

¹ Hurst believed that in nearly all cases the obstruction (due to achalasia) is situated at the sphincter ani, and that the thick walls of the fixed rectum yield less readily than the relatively thin coats of the freely movable pelvic colon, so that the rectum, especially its lower half, does not show the same degree of dilatation. His claims are supported by the finding of muscular hypertrophy of the rectum in a large proportion of the cases which have been examined post-mortem

thickened, and the mesentery of the colon is elongated to a considerable extent, and its vessels and nerves are hypertrophied.

The colon is greatly distended, aggravated by the accumulation of gas. It usually contains a large quantity of pulsatous, scybalous or offensive fæces. The mucous membrane is œdematous and in a state of chronic catarrhal inflammation, and is often ulcerated.

Microscopic examination of the wall of the colon shows enormous hypertrophy of the circular muscle, and a variable degree of chronic interstitial colitis, evidenced by fibrous tissue hyperplasia and round-cell infiltration. Degenerative changes in the intramural nerve plexus (Auerbach) have been frequently observed, but whether primary or secondary is still debated.

Whether the distal limit of the dilatation is at the pelvi-rectal junction or the internal sphincter of the anus there is no muscular hypertrophy at these points, nor is there any evidence of mechanical or spasmodic constriction. This is indicated by the observation that a finger or an instrument may be inserted beyond them without encountering resistance.

Pathological Effects. Obstinate constipation is the most obvious effect of congenital megacolon. Many days or even weeks may elapse without an evacuation of any kind being secured, and relief is usually obtained only by extraneous help. In some cases a certain amount of loose offensive fæcal matter is passed each day, but constipation still persists and the bulk of the intestinal contents is often retained; likewise fluid introduced into the colon by a rectal tube is retained.

Megacolon varies in degree and in the age at which it becomes evident. In many, gross distension of the abdomen and visible peristaltic waves are present in the first few weeks of life. In others, progressive tumidity and obstinate constipation persist during months or years. In less severe cases, the only signs of the affection may be a slight, persistent abdominal distension and chronic constipation, which may persist into adult life.

As the disease progresses, distension may assume immense proportions and the abdominal muscles become thin from stretching, the diaphragm (especially on the left side) greatly elevated, and the costal angle widened and its margins everted. The general nutrition suffers, and emaciation, anæmia, and debility ensue. If untreated a fatal issue frequently results in childhood from toxæmia and anæmia. Sometimes complications such as perforation of the colon, intestinal obstruction from strangulation, and intussusception develop, and usually prove fatal.

Ætiology. It is now generally agreed that the dilatation and hypertrophy in megacolon are not due to mechanical obstruction as by valves or by kinking of the colon. It is true that the pelvi-rectal junction may become kinked, but this is believed to be caused by sagging of the elongated colon and is a result, not a cause of the obstruction.

The explanation most compatible with the pathological and clinical features is one which relates the disease to neuro-muscular incoordination resulting from a relative sympathetic overaction. The distal

part of the colon, like the rest of the alimentary canal, is controlled by the autonomic nervous system, from which it receives both parasympathetic and sympathetic fibres. Its parasympathetic supply, which is propulsive in action, is derived from the pelvic visceral nerves which emerge from the sacral nerve roots; its sympathetic supply, which maintains the normal tone of its sphincters, is derived mainly from the lumbar splanchnic nerves of each side, and is distributed along the inferior mesenteric artery and *via* the hypogastric plexus. In congenital megacolon it would appear that the normal co-ordination between the two systems—emptying and filling—is disturbed, and that there is a relative overaction of the sympathetic which exaggerates the normal tone of the sphincters which remain closed, not from spasm, but from inability to relax. Recent clinical and experimental observations have substantiated the validity of this hypothesis. In megacolon, division of the sympathetic nerve fibres of the distal colon is generally followed by relief of the obstruction, but the long established distensibility of the colon persists.

ILEOCÆCAL TUBERCULOSIS

Compared with the small intestine the colon is rarely the site of tuberculosis, and when infection occurs it is almost always of the ileo-cæcal region. The resulting lesion mimics cancer very closely, but its pathological features are very characteristic. It assumes a chronic and hyperplastic form, and occurs in adults between the ages of twenty and forty years. It is rare under ten years, and still more so after the age of sixty. For a reason that is not obvious, females are more frequently the subjects of this form of tuberculosis than males. Often there is a familial history of tuberculosis.

Ætiology. It is generally conceded that this variety of intestinal tuberculosis constitutes a primary lesion, in that there is rarely any evidence of active tuberculosis in the lungs or other organs. Whereas tuberculosis of the ulcerative type in the small intestine is of quite usual occurrence in patients with active pulmonary tuberculosis, ileo-cæcal tuberculosis is very rare.

It is probable that ingestion of tubercle bacilli is the common mode of infection. The occasional presence of ulcers in the colon, infection of the mesenteric lymph glands, and coincident strictures in the small intestine support this mode of origin. The bovine type of tubercle bacillus is held to be responsible.

Morbid Anatomy. The process begins in the submucous or subserous coat of the colon, where tuberculous follicles develop amidst an area of round-cell infiltration. Tubercle bacilli are difficult to demonstrate. Tissue reaction causes abundant proliferation of fibrous tissue, especially in the submucous layer, but often pervading all the coats. Fibrosis is the outstanding pathological feature of the affection, though caseation may occur, but is rarely very obvious. The disease generally starts in the cæcum, and it may extend towards the hepatic flexure. (The ileum is sometimes involved; and the appendix, which is often retracted

towards the cæcum so that it is scarcely recognizable, seldom entirely escapes.

The diseased portion of the colon shows general thickening and coarseness of all its coats, which with much deposition of fat and infiltration of the mesocolon may give rise to an obvious tumour.) Contracture of the mesentery causes puckering of the bowel, which becomes fixed and rigid, and the colon becomes shortened and drawn towards the liver, and, as a result, the ileo-cæcal angle becomes obtuse. The adjacent lymph glands are usually enlarged and may be caseous or calcified.

From contraction of the fibrous tissue the lumen of the colon is reduced to a narrow channel, sometimes at a localized area, but more often over a considerable length. The colic valve is shrivelled and rigid, and may be difficult to identify. The small intestine often is affected by multiple strictures.

The mucous membrane of the colon is thick and oedematous and commonly is thrown into polypoidal folds. Sometimes there are large superficial ulcers with rather raised edges, situated either in the affected part of the bowel or somewhat distal to it; cicatrization of these ulcers may produce strictures of the lumen.

A combination of tuberculosis and carcinoma has been observed in a number of instances, and generally it would seem that a tuberculous infection had been the primary lesion and the cancer of later development.

The effect of ileocæcal tuberculosis is usually to cause obstruction (but acute symptoms may be long deferred.) In some acute obstruction has followed impaction of foreign bodies such as gall-stone or fruit stone. Perforation of a tuberculous cæcum is rare. Clinical diagnosis of ileocæcal tuberculosis may be difficult on account of its close resemblance to cancer. Diarrhoea and melæna are seldom present. (Formation of a cold abscess or of a fæcal fistula several months after removal of the appendix is not an uncommon way in which the underlying disease may be revealed.



FIG. 228. Ileocæcal tuberculosis. The wall of the cæcum and of the distal part of the ileum is greatly thickened as a result of fibrous and fatty infiltration. The ileum enters the cæcum at a very obtuse angle. In this case acute obstruction followed impaction of a plum stone at the stricture.

Chronicity of the symptoms, often with long periods of intermission, may help to suggest the diagnosis. A barium enema may prove helpful by indicating stenosis of the colon over an unusually wide area and the approximation of the ileocæcal region towards the costal margin.

At operation recognition of the tuberculous nature of the lesion may be impossible, unless some additional feature such as caseous glands or stricture of the ileum is present to lend confirmation.

As the effects of this type of lesion are mechanical, extirpation of the diseased segment of intestine is the method of choice; and, as the lesion is generally an isolated one, surgical treatment has no contra-indication.

Tuberculous Colitis. In rare instances the mucous membrane of the colon becomes the seat of widespread tuberculous ulceration. It affects the distal colon and the rectum, which become greatly thickened and œdematous. Though resolution may occur, the disease tends to pursue a very chronic course and often leads to widespread stenosis of the bowel. Cold abscesses and fistulæ complicate the disease in many instances.

DIVERTICULA OF THE COLON

Diverticula of the colon are present in at least 5% of patients over forty years, though they may produce no symptoms and are often discovered accidentally.

Diverticula occur in adults, and males are affected more often than females in the proportion of 2 : 1. The pelvic colon is the commonest site and may be the only part affected, but quite frequently the transverse and the descending colon are involved. The cæcum and ascending colon are seldom the site of diverticula.

Spriggs formulated the features of the early stages of the disease by means of repeated radiographic examinations. From these, he recognized three stages in the development and progress of the disease : (1) a pre-diverticular stage; (2) a stage of formed diverticula—diverticulosis; and (3) a stage when inflammatory changes have occurred—diverticulitis. The early stage may be noted to pass gradually to a more advanced one, or all stages may be present in different parts of the bowel or in a segment of it.

Ætiology. The common occurrence of diverticula at potentially weak points in its wall, such as the point of entry of blood or lymph vessels, supports the belief that they are of the nature of pulsion diverticula, formed as a result of abnormal pressure within the bowel, augmented, maybe, by bacterial infection of the walls and spasm of its circular muscle fibres.

Constipation has been blamed as an important factor in the production of diverticula, on account of the increased tension it imposes on the wall of the colon, but it is present in only half the cases. Spriggs believes that irritation caused by injudicious purgation with resulting stagnation of liquid fæces in the sigmoid is a more likely cause.

The frequency of diverticula in stout subjects suggests that infiltration of the muscular coat of the colon with fat leads to localized weakness which favours pouch formation.

According to Keith, irregular sustained contraction of the colon precedes the formation of diverticula, and this is substantiated by the radiographic appearances of early cases. Probably in many subjects an inherent weakness of the walls of the colon predisposes to the occurrence of diverticula.

Pathological Features. Early stages of the formation of diverticula are best demonstrated in radiograms after a barium enema. One of the first changes is that the affected part loses its normal segmentation and presents a more rigid and spastic outline. Small bead-like projections of recently formed pouches may be detected at several points; and, after a variable period, diverticula may appear in parts of the colon which previously showed only spasticity. In the early stages the pouches are globular in outline and their necks relatively wide, which allows faecal matter to enter and leave them freely. Later the pouches are flask-shaped and their necks are comparatively narrow.

In the early stages the only evidence of diverticulum formation is a slight superficial corrugation of the serous surface of the bowel. In typical cases, at a later stage, the colon is studded with pea-like projections, often coated with fat. Only the larger pouches are detectable on the exterior. Any part of the circumference of the bowel may be affected, but points of entry of blood vessels and the appendices epiploicæ are favourite sites, and the tæniæ coli are rarely affected. Each diverticulum consists of a protrusion of mucous membrane into or through the muscular coat, and in all but the smaller pouches muscle fibres are present only at the neck. Pellets of inspissated faeces sometimes form in the interior of diverticula (stercoliths) and may cast a shadow visible on radiography. Seen from the interior the mouths of the diverticula may be circular or slit-like, but more often on account of inflammatory œdema of the mucous membrane they can be detected only when the bowel is stretched or when faecal matter is expressed from them. Localized thinning of the colon is noted at the neighbourhood of the most recently formed diverticula.

Secondary inflammatory changes in the walls of the diverticula (diverticulitis) and in the adjacent colon (peridiverticulitis) are common, and it is from these changes that symptoms commonly arise.



FIG. 229. Diverticulitis. The colon is segmented in a ladder-like fashion and all the coats are the seat of fibrous tissue proliferation.

(By courtesy of Mr. J. W. Struthers.)

The inflammatory changes are often slight and are associated with a round-cell infiltration and fibrous tissue proliferation, and, what is very characteristic, the accumulation of quantities of fibro-fatty tissue. The overgrowth of fibrous tissue and fat is most evident in the appendices epiploicæ, in the mesenteries, and in the subserous or the submucous coats of the bowel and is often so great as to conceal the diverticula completely. Contraction of the newly formed fibrous tissue may lead to stenosis of a segment of the colon, or may



FIG. 230. Portion of same specimen as depicted in Fig. 229, to show the orifices of the diverticula.

(By courtesy of Mr. J. W. Struthers.)

involve a considerable portion, giving it a rope-like and rigid appearance. When stenosis becomes extreme, acute or chronic intestinal obstruction may result. Similar changes cause shortening of the mesocolon and lead to abnormal fixation or to angulation of the colon, and increase the difficulties of operation. Contraction of fibrous tissue around the neck of the diverticula leads to retention of faecal matter and favours the occurrence of inflammation. Ulceration of a diverticulum by infection may terminate in perforation and lead to general peritonitis, or more commonly a localized abscess. The abscess usually points in the left iliac fossa, but it may perforate the bladder and form a colo-vesical fistula. Ulceration of the colon is rare and therefore hæmorrhage and mucous discharge are not usual.)

Acute exacerbations are apt to occur in diverticulitis, and are often associated with a mild degree of local peritonitis with attacks of pain in the

left side of the abdomen.

Subjects of diverticulitis commonly suffer from lumbago, from spondylitis, and from other chronic lesions of ligaments and joints.

Differentiation from malignant disease is difficult when diverticulitis gives rise to a palpable tumour. Cancer and diverticulitis have been coexistent occasionally, but the association is too infrequent to be of practical importance. In diverticulitis great help is obtained from radiographic examination after a barium enema: barium may be retained in diverticula for many weeks.

The pathological changes in connexion with diverticulitis may be so widespread as to preclude resection, while the infection of the bowel wall renders it unsuitable for primary suture.

Congenital Diverticulum of the Cæcum. This type of diverticulum is rare. It is solitary and emerges from the colon on its medial aspect immediately above the ileocecal valve. It is of developmental origin.

usually small, and has a complete covering of muscles. The neck of the diverticulum is narrow, a factor which predisposes it to inflammatory complications similar to those in appendicitis. In some instances the inflamed diverticulum becomes inseparably bound to the colon and a mass develops which may simulate carcinoma.

SIMPLE TUMOURS OF THE COLON AND RECTUM

Simple connective-tissue tumours are rare in the large intestine. A submucous lipoma is commonest and generally occurs in the cæcum, where it may give rise to obstruction or simulate appendicitis.

Commoner and more important are the epithelial tumours, which take the form of papillomata. Dukes found that in 127 subjects post-mortem they were present in 10%, the incidence increasing after the age of forty.

Papillomatous growths vary in appearance, and three types may be recognized: (1) a smooth pedunculated polypus; (2) a villous papilloma; and (3) diffuse polyposis.

A pedunculated polypus occurs frequently in the rectum of children. Arising as an adenoma of the mucous membrane it becomes pedunculated as a result of peristalsis and it may be protruded at the anus. Its surface is smooth or mulberry-like and its colour pink or red according to the degree of congestion. In children this tumour, which is adenomatous in structure, is simple; but in adults it shows a tendency to become malignant.

A villous papilloma may be flat or pedunculated. Its size varies from that of a pin's head to a large button; its surface may be smooth, shaggy, or mammillated. A papilloma is often solitary, or there may be several hundred scattered over a segment of the colon.



FIG. 231. Carcinoma of the pelvic colon: dual growths. Note the pedunculated papilloma above the distal tumour.

(Department of Surgery, University of Edinburgh.)

Microscopic examination shows epithelium composed of columnar cells supported by a core of connective tissue derived from the submucosa. The blood vessels are thin walled and often dilated.

Diffuse Polyposis. When the colon is covered diffusely by papillomata the resulting disease is known as diffuse or multiple polyposis or colitis polyposa. The polypi are preceded by a generalised hypertrophy of the mucous membrane and submucosa, as though it were the seat of irritation. The descending and pelvic parts of the colon are the most often affected, but the cæcum and rectum may sometimes be involved.

Diffuse polyposis is a precancerous condition. It is common in childhood. Nothing definite is known of its ætiology, but it is well known that it is often hereditary, as also is the predisposition to cancer. The polyposis is accompanied by a variable degree of colitis, so that diarrhœa with blood in the stools is usual and may lead to great depletion.

Relation to Cancer. Polypi and cancer in the colon frequently coexist. In specimens of cancer of the colon removed at operation Dukes found papillomata in 75%: they occurred generally adjacent to the tumour and were often numerous. Thus it appears that the association of benign papillomata and cancer in the colon is very important and more than accidental.

That a simple papilloma may occasionally become malignant is known, but more often the malignancy develops elsewhere in the bowel. The experiences of Lockhart-Mummery afford evidence that an adenoma may herald the development of carcinoma: in a series of 50 cases, observed and treated for many years, carcinoma developed in no less than twelve.

CANCER OF THE COLON

The colon is frequently affected by cancer. The disease arises in later life, and is usually of slow progress and metastasizes, if at all, at a late stage. Occasionally it affects younger persons and then progresses more rapidly and disseminates earlier.

In over 40% of cases the tumour affects the pelvic colon; less often it affects the ascending, the transverse and the descending colon (in that order of frequency). The cæcum proper (*i.e.*, the portion of the colon below the ileocæcal valve) and the splenic flexures are each affected in about 5% of cases. The hepatic flexure is a rare site. Occasionally there are two or even more tumours, apparently distinct, either a few centimetres apart or in different portions of the colon. Rarely the removal of one tumour is followed several months or even years later by the development of a second or even a third "primary" growth.

Microscopic Structure. The carcinoma has the structure of columnar-cell carcinoma, and the histological features vary somewhat according to the degree of differentiation of the cells and the amount of fibrous tissue stroma. Generally the columnar cells are arranged in irregular acini, but sometimes the acinar arrangement

is lacking and they lie in solid groups, interspersed with a scanty areolar stroma. Not infrequently the tumour undergoes mucoid (colloid) degeneration, and this character is usually reproduced in metastases.

Types of Cancer of the Colon

According to their naked-eye characters, two principal types of cancer of the colon are recognized, (1) the proliferative type, (2) the annular sclerosing type. The second is the commoner, although intermediate types are frequent.

(1) **The proliferative type** occurs usually in the cæcum or the ascending colon, less often in transverse and distal colon. It is a bulky tumour, which projects into the lumen as an uneven, nodular mass. Its surface ulcerates, leading to hæmorrhage and infection. The tumour does not encircle the bowel, but obstructs rather in virtue of its bulk. Since the proximal part of the colon is capacious and its contents fluid, obstruction does not supervene until late, and in some the only effects during a long period are anæmia and cachexia aggravated by infection. The irritation from the tumour and the adjacent inflamed mucous membrane may lead to diarrhœa with abundant mucus in the stools.



FIG. 232. Adeno-carcinoma of the colon. The tumour is composed of columnar, mucus-secreting cells disposed in irregular acini.

(2) **The annular type** occurs in its characteristic form in the distal part of the bowel, especially in the pelvic colon, but it may occur more proximally, for example, in the transverse colon or at the mid-part of the ascending colon. It grows slowly, and forms a small tumour, which does not project much into the lumen, but infiltrates the wall of the bowel, encircling it. On account of the slow infiltrating character and the accompanying fibrosis, the tumour leads to a localized constriction of the colon, as by a cord (*string stricture*). On the mucous surface the growth remains circumscribed, with little longitudinal extension, and ulceration may be long delayed and never very extensive. The affected part is rendered stiff, and its lumen may be reduced to a very fine channel.

On account of the absence of much ulceration, this type for long

gives rise to little disturbance of health, and generally the first effects are progressive, and ultimately acute, obstruction.

Pathological Effects

Mention has been made of several of the effects of colon tumours, for example, hæmorrhage and toxic absorption, which are more pronounced in the proximal

portion of the colon. Obstruction is most likely to occur in the annular type, especially when it is situated in the distal part of the colon, where the lumen is of small calibre and the faecal content solid. Generally, the obstruction arises insidiously, and is evidenced by increasing constipation and progressive abdominal distension. Eventually obstruction may be complete, and frequently that seems to be the first evidence of the disease. Complete obstruction may be due to stenosis of the bowel, but often it is precipitated by impaction of a faecal mass or foreign body in the narrowed part. On rare occasions obstruction results from intussusception of the affected segment into the bowel distally.

In progressive obstruction the gut proximal to the constriction is hypertrophied and later dilated.

Dilatation affects espe-

cially the cæcum, which is distended by fluid faecal matter and gas. Putrefaction of retained faecal matter favours development of the stercoral ulcers, which may give rise to localized peritonitis or may perforate, causing fulminating diffuse peritonitis. Perforation of the cæcum is especially likely to occur when the abdomen is opened and the colon is deprived of the support of the abdominal walls. Longitudinal splits in the tænia coli occur frequently when there is great distension. Ulceration close to the site of cancer may cause infection of the retrocolic areolar tissues, and may lead to an intraperitoneal or extraperitoneal abscess.



FIG. 238. Papillomatous type of carcinoma of pelvic colon.

Avenues of Extension

Cancer of the colon generally grows slowly. It extends principally by direct infiltration of adjacent tissues and, later, by invasion of lymph vessels and glands. Metastasis to distant sites, such as the liver, is a late feature.

Direct Infiltration. At first the growth is limited to the mucous and submucous coats, and in these layers it tends to spread mainly at right angles to the long axis of the gut. This is especially evident in the annular type of tumour. Later the growth penetrates the muscle coat and may erupt at the peritoneal surface or invade the retroperitoneal tissues and the muscles of the abdominal wall. In some cases a growth erupting at the peritoneal surface disseminates to many parts of the peritoneal cavity and gives rise to multiple metastases, especially in the omentum, on the surface of the ovaries, or on the pelvic floor. In others, as a result of superadded infection or direct infiltration, the affected portion of bowel becomes adherent to other viscera, particularly the small intestine or its mesentery, the bladder, or the uterus or its appendages, so that at operation sacrifice of parts of these organs may be necessary.

Lymph Spread. Tumours in the proximal and distal parts of the colon differ considerably in their paths of lymph vascular extension. The normal absorptive function of the proximal colon demands an abundant lymph drainage, and consequently there is a large number of glands in relation to this part. The distal colon, having no absorptive function, possesses fewer glands.

For the colon the lymph vessels and glands are disposed along the main arteries. A few glands (epicolic) lie on the surface of the gut, but the more important ones lie within the mesenteries or in the retroperitoneal tissues. In the cæcum and the ascending colon the glands along the ileocolic vessels are involved; in the transverse colon the glands in the mesocolon, and rarely, if the omentum is adherent, the gastro-epiploic glands; in the distal part of the colon the glands along the inferior mesenteric vessel and its branches are affected.

The differences in lymph drainage of the proximal and the distal colon are reflected in differences in the treatment and in the prognosis in the two situations. The numerous and relatively distant lymph glands in relation to the proximal colon necessitate a wider resection of the gut, and render subsequent recurrence more probable. The paucity of glands in relation to the distal colon justifies a local resection, and greater expectation of permanent freedom from disease.

Blood Spread. Metastases by the blood stream seldom occur except in the advanced stages of the disease. Occasionally, however, they may do so earlier, and sometimes metastases develop in the liver, even before extension of the disease locally.

STRICTURE OF THE RECTUM

Stricture of the rectum may result from traumatism or follow any type of ulcer, including malignant disease. Apart from these there is a type of rectal stricture which has long been recognised, though until

recently its aetiology was obscure. It nearly always occurs in women and originates as a hyperplastic fibrosis in and around the connective tissue of the rectum. In the course of years the scarring extends and leads to a long and eventually very tight stricture, situated usually

2 to 3 inches from the anus. The mucous membrane may remain free from ulceration until a late stage. Finally there may be fistulae on the skin surface, and elephantiasis of the vulva may develop.)

This type of stricture of the rectum was formerly ascribed to gonorrhoea or syphilis, but though it is possible that occasional cases have such an origin, recent observations prove that most are due to infection by the virus of lympho-granuloma venereum. The infection, which is transmitted as a venereal disease, is seen most often in tropical or Mediterranean countries, but occasionally is brought to this country by persons returning from abroad. In man the rectal manifestation of the disease is rare and when it occurs a direct contagion may be assumed.

In diagnosis the Frei reaction (an allergic reaction induced by intradermal injection of extracts of fresh infective material) is almost specific.

CARCINOMA OF THE RECTUM

Cancer of the rectum differs only slightly in its pathology from cancer in other parts of the colon, but on account of its position it is more convenient to consider it separately.

Carcinoma of the rectum is said to be four or five times as frequent

FIG. 234. Stricture of the rectum. The lumen is narrowed by a stricture almost 5 inches in length. The mucous membrane is extensively ulcerated whilst the outer coats are infiltrated with a thick layer of dense fibrous tissue.

(By courtesy of Professor J. W. S. Blacklock.)

as in the colon. It affects the two sexes with about equal frequency, and most often between forty and sixty years of age, although it is not very uncommon at an earlier age.

The growth begins generally at the pelvi-rectal junction, where the tumour is just out of reach of an examining finger. It may be



(situated at, or just below, the peritoneal reflection. That relation is of importance because, when the growth abuts on the peritoneum, metastases may occasionally be diffused over a wide area by the subserous lymph vessels, or there may be a large plaque of disease in the peritoneum of the rectovesical pouch. Such highly placed growths are almost always of annular type, similar in character and in effects to those of the colon.)

In the ampulla the cancer may be of a cauliflower type, or it may be sessile and extensively ulcerated. There are associated papillomata in about 80% of cases. Generally, tumours which grow towards the lumen of the bowel are less malignant than the flattened type which penetrates the rectal walls at an earlier stage. An exception to this general behaviour is the primary mucoid type of carcinoma, which is usually a bulky tumour of rapid growth, with marked invasive characters and a tendency to early metastasis in glands and by the blood stream.

Microscopically, the tumour is usually of columnar-cell type. There is considerable variation in different tumours, and in parts of the same tumour, and examination of only part may lead to fallacious conclusions. Within certain limits the histological appearances provide a fairly reliable indication of its grade of malignancy. The common appearance is one of ill-formed acini or alveoli, composed of cells of primitive type with many mitoses. More benign types may give the impression of a simple adenoma. The mucoid type, which is the most malignant, is composed of irregularly arranged cells distended with lightly staining cytoplasm (signet-ring pattern): it represents a malignant hyperplasia of mucus-forming cells, and is very malignant and should be differentiated from the relatively benign types in which a high degree of differentiation is suggested by elaboration of mucus within the irregular acini of the tumour.

In the majority of instances, carcinoma of the rectum is of relatively slow growth, and for long remains confined to the mucous membrane, sometimes for as long as a year. There are three methods of spread: (a) by direct infiltration, (b) by the lymph vessels, and (c) by the blood stream.

(a) *Spread by Direct Infiltration.* Tumours situated at the pelvic-rectal junction encircle the wall of the rectum producing stenosis. At a late stage they spread through the rectal wall and reach the parietal peritoneum, where they may give rise to secondary nodules; or spread to adjacent viscera such as the bladder, the ureters, or the uterus.

A carcinoma in the ampulla grows centrifugally, especially when of the crateriform ulcer type. Occasionally nodules appear at a distance from the parent tumour, presumably the result of localized spread in the submucous lymph channels.

The muscular coats are penetrated first at the central or oldest part of the tumour, and the growth then spreads in the fat and areolar tissue around the rectum. At this stage it lies within the fascia propria of the rectum, and not infrequently extends in this plane for a considerable distance without involvement of adjacent organs, or even of the regional lymph glands. Later, when the fascial covering is invaded and the pararectal tissues are invaded the rectum may become

fixed to the sacrum or to neighbouring viscera. By direct spread the base of the bladder, the seminal vesicles, or the prostate may be involved, and in the final stages fistulæ may develop. In women the posterior vaginal wall is often implicated. Occasionally abscess formation occurs in the pelvic cellular tissue or in the ischiorectal fat, from leakage at the site of the tumour.

(b) *Spread by the Lymph Vessels.* Examination of specimens removed at operation shows that the regional lymph glands are the seat of metastasis in about 50% of cases. Usually only a few glands are affected, but sometimes, and especially in rapidly growing tumours (even at an early stage), there may be very widespread involvement. In the majority of cases the glands are unaffected until the tumour has penetrated the muscular wall of the rectum. Enlargement of the glands from infection is common and greater than usually occurs from metastasis.



FIG. 235. Cauliflower type of carcinoma of rectum.

(Department of Surgery, University of Edinburgh.)

The glands are situated in the perirectal fat and within the fascial sheath, and are disposed around the lower part of the superior hæmorrhoidal artery and its terminal branches, and when the rectum is removed (enclosed in its sheath) the glands are included. The affected glands are found usually a short distance above the level of the tumour, but in a few instances, those at a higher level may be the site of metastasis without involvement of those adjacent to the tumour; but metastasis in glands higher than the main trunk of the superior hæmorrhoidal artery is

exceptional. In the radical operation for carcinoma of the rectum removal of the higher glands should be ensured by ligation of the superior hæmorrhoidal artery at as high a level as possible.

Spread of carcinoma beyond the rectum by a general lymph vascular permeation appears to be prevented by the investing fascial sheath; therefore, involvement of the peritoneum, the levator muscles, and the anal sphincters is very rare. This justifies a fairly circumscribed removal.

As in carcinoma of the breast, so in carcinoma of the rectum, the presence of glandular metastases has an important relationship to the probability of local or general recurrence after operation. Thus Gabriel found that there was a 19% survival after three years, in cases in which metastasis had been demonstrated, as compared with 86% in cases in which the carcinoma was confined to the walls of the rectum and in

which there was no metastasis. Even in cases with extra-rectal spread and without metastasis the survival rate (over the same period) was 78%, which signifies that glandular metastasis is more important in prognosis than the extent of the tumour.

(c) *Spread by the blood stream* is infrequent, but is not necessarily a late feature of the disease. It occurs most frequently in rapidly growing tumours in young subjects. Generally the liver is involved alone; but in rare instances metastases are found in the lungs and other organs. When recurrence takes place after operation the liver is usually affected. Prior to radical operation the liver should be examined because, thereby, a needlessly severe operation may be avoided.

Carcinoma of the rectum is often latent until an advanced stage of the disease, and, until ulceration of the tumour occurs, symptoms are

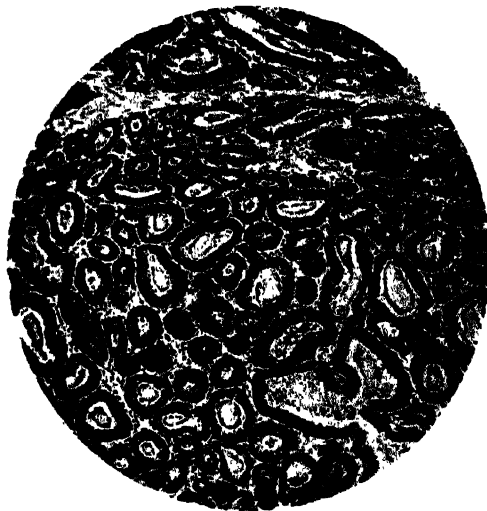


FIG. 236. Cancer of the rectum. The tumour is an adeno-carcinoma composed of columnar cells arranged in fairly well-formed acini.

frequently absent. Pain is a late feature, but ultimately it may give rise to great distress. Ulceration results in abundant mucous discharge and bleeding, and, sometimes, hæmorrhage is very profuse and even fatal. When the growth is placed high in the rectum obstruction of the colon results and may be acute. Death has occurred from perforation of a rectal carcinoma into the peritoneal cavity, but it is a rare complication. Involvement of the pelvic nerve trunks may occur at a late stage.

CARCINOMA OF THE ANUS

Cancer at the anus generally arises at the junction of the columnar and squamous cell lining. Usually there is no obvious precancerous lesion, but occasionally it is preceded by a fissure, an ulcer or a burn.

The tumour is a squamous-cell carcinoma; it may be papillary in type or a crateriform ulcer. It does not tend to spread up the rectum, but it may invade the skin of the perineum extensively. Involvement of the anal sphincter may lead to incontinence. Metastatic growths develop in the inguinal lymph glands. In many instances the disease is first seen when successful treatment is impossible.

MELANOMA OF THE RECTUM

This type of tumour is of rare occurrence. It arises from the skin within the anal canal as a hard nodular mass dark in colour. It tends to grow upwards into the rectum, the coats of which may be extensively invaded. There is variation in its degree of malignancy: some tumours remain localized and grow only slowly, others grow rapidly and metastasize widely both to the lymph glands and by the blood stream. The inguinal glands are sometimes the seat of secondary deposits. Pigmentation of the regional glands may be due simply to phagocytosis of pigment granules, but is more often due to cellular metastases.

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CHAPTER XXV

DISEASES OF THE VERMIFORM APPENDIX

APPENDICITIS

THE history of appendicitis requires no recital, for almost in its entirety it comes within living memory. Until 1885 the disease was rare, yet within twenty years it had attained the position of being the most common of all acute abdominal illnesses. At first consideration it might be supposed that such a remarkable change in incidence, occurring at the time when the surgery of the abdomen was advancing most quickly, might be attributable principally or entirely to a keener recognition of the disease ; but, as Rendle Short has shown, this is not so—the increase is actual, not merely apparent.

Although appendicitis was known in the eighteenth century, it received little recognition until 1886, when Fitz described a long series of cases, distinguished it clearly as the commonest cause of “perityphlitis,” and gave it the name now universally adopted. From 1886 to 1905 there was a great increase in the frequency of the disease, first noticeable in the cities and towns of Great Britain and America, and later in the country districts ; since 1905 the frequency has remained unchanged.

Appendicitis is almost entirely a disease of the Western world, and particularly of Great Britain and America. In Denmark, Spain and Italy it is still uncommon, in the rural districts of Rumania and other parts of Eastern Europe it is distinctly rare, and amongst the native populations of many parts of Asia and Africa it is almost unknown. In general, the disease is one of modern civilized life, although a few highly civilized races, *e.g.*, the Japanese, remain free from it. There is ample evidence that its incidence does not depend upon any racial, climatic or geological factors, but is intimately related to modern developments in the diet or mode of life of the Western world. When natives of the East adopt the dietary of Great Britain or America they become liable to appendicitis, but Europeans living in the East do not lose their susceptibility, for they retain their Western customs. In the United States of America the coloured people in country districts of the south maintain their traditional ways of living, and remain free from appendicitis, but those who migrate to the cities or northward and adopt the habits of the whites lose this immunity.

There is evidence that the increased frequency of appendicitis is associated with the more general use of a diet rich in proteins. In Great Britain and America the period 1885—1905 was one of greatly increased prosperity for the industrial classes, and a correspondingly greater demand for an animal diet ; moreover, a close correspondence

between meat-eating and appendicitis is indicated by the rarity of the disease in communities where the diet is principally vegetarian, as in the rural districts of Eastern Europe and Asia, and in the poorhouses, prisons and asylums of this country. But the consumption of proteins cannot be the only factor, for meat-eating was indulged in before 1880 ; as Rendle Short has pointed out, the "Roast Beef of Old England" has been appreciated for centuries, and, indeed, from contemporary accounts, too well ! Constipation might be regarded as a predisposing factor, but, as Pepys bears witness, also is no modern development. According to Rendle Short, the essential difference between our food and that of our forebears lies in the relative paucity of cellulose and in the consequent diminution in the bulk of the excreta ; and it is possible

that this, in conjunction with a high protein content of the diet, is responsible for the increased frequency of appendicitis, the protein excess permitting increased putrefaction in the lower bowel, and the lack of cellulose leading to inspissation of the appendicular content.

Experimentally, Wilkie demonstrated in cats the important relationship of a protein diet to infections in the lower bowel. The cat has no appendix, but an isolated portion of the lower ileum may be fashioned to represent one. If this "artificial appendix "



FIG 237. Section of the appendix (low power). showing a large lymph follicle situated immediately deep to the epithelium of the mucous membrane.

(Laboratory of Royal College of Physicians of Edinburgh.)

be obstructed, by ligature of its proximal end, the morbid changes that follow depend partly upon the nature of the animal's diet. If the diet has been entirely carbohydrate for a long period, the pathological changes develop slowly and the cat may survive several days ; but an animal on a meat diet may die within twenty-four hours.

Ætiology of Appendicitis. Apart from the question of diet, which has already been considered, there are three important factors in the ætiology of appendicitis, (1) the structure of the appendix, (2) its contents, and (3) its shape.

(1) *Structure.* Lymphoid tissue abounds in the wall of the appendix, where it forms definite follicles in the mucous and submucous coats. It appears in quantity shortly after birth, it is most abundant in childhood and adolescence, and after the age of thirty it tends, like lymphoid tissue elsewhere to atrophy. It probably constitutes a barrier against

infection, which, as elsewhere, may be overcome if the bacterial attack is overwhelming.

(2) *Contents.* Foreign bodies are very prone to lodge in the appendix. The foreign bodies include a wide variety of objects, animal, vegetable or mineral. By far the most common are soft, putty-like concretions composed of faecal matter, bacteria, fats, soaps and lime salts; such concretions arise when the bowel content becomes dry and inspissated, and when the appendix, from narrowing of its lumen, from atony of its muscular coat, or from other cause, is unable to expel. Less often other foreign bodies are found, date stones, seeds of various kinds, pins and beads, and even teeth, but their importance has been greatly exaggerated. Those who eat much game often swallow small lead shot, which may lodge in the appendix, but they rarely precipitate an acute attack.

(3) *Shape.* The appendix is a narrow *cul-de-sac*, and is very liable to become obstructed. From the teaching of Wilkie it is now clearly recognized that one of the most important factors in appendicular disease is obstruction of its lumen. The appendix develops as a conical, relatively wide-mouthed protrusion from the caecum, and in many animals, such as the rabbit, it remains so throughout life. In man the orifice of the appendix, which is still wide during infancy, gradually narrows, and becomes partly occluded by a valve-like fold of mucous membrane; it is partly for this reason that appendicitis is rare in infancy, but common after the first few years of life, when a small lesion may obstruct the narrow lumen. In later life the appendix atrophies and diminishes in size, and consequently appendicitis is again more rare. Stenosis of the appendix predisposes to obstruction. Such a stenosis may be congenital, *e.g.*, from fixation of the appendix in the retrocaecal position, or from kinking by such a band as the genito-mesenteric ligament, which tacks down the mid-point of the appendix towards the pelvis; or the stenosis may be acquired, from inflammatory fibrosis in the appendicular wall, from kinking by a shortened meso-appendix, or from inflammatory adhesions.

No one who has carefully examined acutely inflamed appendices can have failed to note the regularity with which an obstruction of the lumen delimits the inflammatory changes. The obstruction is due usually to impaction of a concretion or other foreign body at a place where the lumen is narrowed, but occasionally no foreign body is present and the obstruction is due either to fibrosis or to inflammatory swelling. The site of obstruction within the lumen of the appendix determines the extent of its involvement.

Acute Appendicitis

In appendicular disease (as in many others) a cumbersome nomenclature is still evident, and few descriptions are, without elaborate classifications of catarrhal, suppurative, gangrenous or phlegmonous appendicitis, and appendicitis with perforation, with abscess, or with peritonitis. With a clearer appreciation of the causes of the disease it becomes evident that many of these "types" are

merely stages of one process, modified, on the one hand, by variations in the virulence of the disease and, on the other hand, by the defensive forces of the body ; the particular " type " of affection in any individual is merely the resultant of these two processes. Appendicular disease should be studied as a continuous story rather than in serial form.

The severity of the disease is greatly modified and aggravated by obstruction of the appendicular lumen. If the appendix remains unobstructed in an inflammatory attack, the disease usually pursues

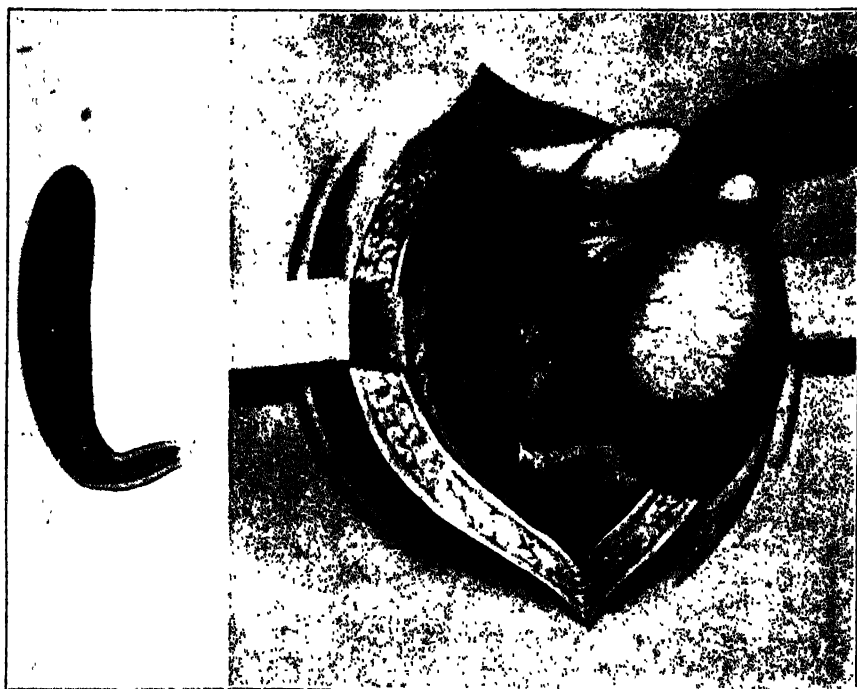


FIG. 238. Acute appendicular obstruction, due to impaction of a concretion at the point at which the retrocaecal appendix is kinked. The appendix distal to the obstruction is distended and gangrenous.

(Department of Surgery, University of Edinburgh.)

a mild course ; but when the lumen is occluded any pre-existing or potential infection is intensified, for inflammatory products remain pent up, and gangrene or perforation may rapidly supervene.

Appendicitis without Appendicular Obstruction. The organisms principally concerned in appendicitis are colon bacilli, streptococci, and anaerobic organisms. Generally they are derived from the lumen of the large bowel, infecting the appendix *via* its lymphoid tissue ; it has been suggested that some organisms, particularly streptococci, may reach the appendix through the blood stream from some distant focus.

The disease commences in the lymphoid follicles of the mucosa ; it may remain limited to this membrane—*catarrhal appendicitis*—but almost invariably it spreads to involve the other coats of the wall. The mucous membrane becomes thick, cedematous and congested ; hæmor-

rhagic spots and small erosions appear on its surface, and the whole appendix becomes swollen and turgid. With further extension of the infection the serous surface becomes covered with fibrinous exudate, and local mild peritonitis develops. The disease usually does not progress acutely, but occasionally, particularly where a concretion or other foreign body causes pressure upon the diseased wall, a perforation or a peri-appendicular abscess may occur. At any part of the course, moreover, the lumen of the appendix may become occluded by swelling of the mucosa; and with the onset of an obstructive element graver developments take place. If uncomplicated, the disease may subside, but complete resolution, with return to the *status quo ante*, is uncommon; infection is likely to recur, often with enhanced severity, and inflammatory scarring may lead to stricture and subsequently to an obstructive lesion.

Appendicitis with Appendicular Obstruction. This is a considerably more dangerous type of disease, and forms a large proportion of the cases seen at operation. In its pathology it resembles one form of acute intestinal obstruction, for the appendix becomes a closed loop of bowel containing septic faecal matter.

The effects of acute appendicular obstruction depend upon the infective nature of the matter in its lumen and also upon the presence of much organic faecal matter which may readily putrefy. If infection is mild the appendix becomes thickened, and gradually distends with mucopurulent fluid to form a *mucocoele*, one variety of chronic appendicitis (*q.v.*). If the infection is of greater degree the appendix becomes distended with pus—*empyema of the appendix*—and later may become gangrenous and perforate. If the infection is highly virulent and the appendix contains much faecal matter, gangrene and perforation may occur with extreme rapidity, causing widespread peritonitis—*fulminating appendicitis*.

Perforation of the appendix through a gangrenous spot is an important event in the progress of the disease, for if the appendix has previously been distended the grossly infected contents are forced out and will contaminate surrounding tissues. In rapidly progressive cases perforation may occur within a few hours of the onset of the attack, and may lead to widespread peritonitis; or, if the appendix is surrounded by adhesions a local abscess may result.

Changes around the Appendix. These depend upon the intensity and virulence of the infection and upon the existence of adhesions that may limit the spread of the disease.

If the infection is rapid and virulent, as when the appendix perforates quickly, or when a slowly forming abscess suddenly bursts its protective wall, a widespread peritoneal infection ensues. The peritonitis commences first around the appendix and over the pelvic organs and pelvic coils of ileum; later it spreads into the upper part of the abdomen. If resistance is great, the peritoneal exudate becomes thicker, and adhesion of opposed serous surfaces leads to loculation of the pus. In these cases intestinal obstruction is a common and grave complication.

Should the infection spread more slowly, it excites a vigorous reaction

on the part of surrounding tissues, and a dense protective barrier forms against further extension of the disease. A lymph exudate is poured out, containing many pus cells but few or no organisms. The serous surfaces become ingested and adhere, the great omentum envelops the appendix like a thick mantle, and neighbouring coils of intestine become immobilized to form a barrier around the infective focus.

At this stage the infection may subside, leaving a large inflammatory mass, perhaps the size of an egg, which slowly diminishes. In the course of time many of the adhesions resolve, and the appendix may become shrivelled and fibrotic; often, however, it is liable to recrudescence of the infection.

Appendicular abscess. If the disease progresses, though limited by the protective barrier, there develops a localized appendicular abscess, containing thick foul-smelling pus. The abscess may be small, buried in a mass of adhesions, or it may attain considerable size, displacing the neighbouring intestines as it grows. If untreated it may open into one of the hollow organs, the cæcum, rectum or bladder, or it may eventually reach the skin surface; occasionally, however, it bursts into the general peritoneal cavity and causes widespread, rapidly fatal peritonitis. The situation of the abscess depends upon the position of the appendix. Most often it is in the right iliac fossa just medial to the anterior superior spine; not infrequently it is in the pelvis, or behind and lateral to the cæcum; but it may be in the region of the gall bladder, in the mid-line below the umbilicus, or even on the left side.

Appendicitis due to Parasites. *Threadworms* (oxyuris vermicularis) are of particular interest as a cause of appendicitis. They are rarely responsible for acute or fulminating inflammations, but are not uncommon, particularly in children, in association with mild recurring attacks. The parasites are usually multiple, and often collected together in a small clump close to the base of the appendix, which may contain a little purplish or prune-coloured fluid. Female parasites are more common than male, and are often heavily laden with ova, and Still has suggested that they use the appendix as a breeding place. It might be supposed that threadworms would predispose to appendicitis merely as irritating foreign bodies, but it has been shown that there is an actual invasion of the mucosa by the worms, which in serial sections of the appendix can be seen lying deep in the wall and even penetrating as far as the muscular coat. In this way they produce minute ulcerations and hæmorrhages which readily predispose to infection. Clinically threadworms give rise to recurring mild attacks in which the predominating feature is the occurrence of colicky pain diffused over the abdomen, with little pain or tenderness on pressure over the appendix. Occasionally the attacks are febrile, and the temperature may even mount to 102–108° F.

A *round worm* (ascaris lumbricoides) may enter the lumen of the appendix and lead to appendicular colic or mild appendicitis. The worm occupies the whole lumen of the appendix. If its presence be unrecognized, subsequent histological examination of the transversely sectioned appendix will reveal a remarkable appearance as of a double-

barrelled tube, each barrel lined by intestinal mucous membrane, the outer one formed by the appendix, the inner by the gut of the parasite.

Cause of Pain in Acute Appendicitis. The cause of the pain in acute appendicitis forms a subject of great interest in relation to the general physiological aspects of abdominal pain. The appendix, like other viscera, is but little sensitive to ordinary stimuli, and when the abdomen is opened under local anaesthesia it may be handled without discomfort, yet the pain of acute appendicular disease may be intense.

One of the first important studies of abdominal pain was made by Ross in 1887. He formulated the hypothesis that visceral disease may give rise to two varieties of discomfort, namely, true splanchnic pain felt in the viscus itself, and somatic or referred pain felt in the parietes. The existence of splanchnic pain was denied by Mackenzie, who held that all abdominal pain is somatic, *i.e.*, referred to the parietes. In a number of papers which appeared from 1892 to 1906 Mackenzie put forward the theory that pain of visceral disease results from a "viscero-sensory reflex" action. Impulses extend from a viscus along its afferent autonomic fibres to the spinal cord, and though these impulses are themselves unperceived by the brain they give rise to painful sensations by "overflowing" to neighbouring parts of the cord and irritating adjacent sensory nerves. According to this view, impulses from the appendix reach the eleventh or twelfth thoracic segments of the cord and "overflow" to sensory nerves at this level, so that they are appreciated by the brain as impulses originating in the lower abdominal wall. Similarly the hyperaesthesia associated with some abdominal diseases could be regarded as due to over-excitability of the sensory nerves of the parietes, and muscular rigidity could be regarded as resulting from "overflow" stimulation of motor nerves (visceromotor reflex).

Mackenzie's conception, however, fails to explain many aspects of abdominal pain, and there are fundamental objections to the whole theory of viscerosensory and visceromotor reflexes. The evidence against these views, exemplified in a study of the pain of acute appendicitis, has been discussed by Morley. He points out that there can be no doubt, as Hurst has shown, that true splanchnic pain does exist. Painful stimuli can originate in hollow viscera either from spasm or increase of tension of the muscle fibres. When the stimuli arise in any portion of the mid-gut (which includes the appendix) such pains, whether colicky from peristalsis or continuous from distension, have two characteristic features; (1) since the visceral nerve supply is not strictly localized the pains are ill-defined, and (2) since developmentally the mid-gut is a median organ, the pains are felt principally near the mid-line.

Kinsella has recently supported these views as a result of direct observations made during the performance of appendicectomy under local anaesthesia. He has shown that whereas the appendix, like other viscera, is insensitive to localized injury, *e.g.*, by crushing with a forceps, considerable pain is caused by squeezing the whole organ between the fingers. Such pain is almost always referred to the midline in the umbilical region.

It is a matter of everyday observation that in acute appendicitis there are usually two distinct varieties of pain. In early stages of the attack the pain is ill-defined, and principally felt close to the mid-line, around the umbilicus or in the epigastrium. It is obvious that this initial pain of acute appendicitis has the characteristics of true splanchnic pain: it may be colicky from excessive peristalsis or continuous from increased intra-appendiceal tension. Early colicky pain in acute appendicitis invariably indicates an obstructive lesion.

The later variety of pain in appendicitis, which usually becomes evident a few hours after the onset of an attack, is entirely different in situation and character from its forerunner. It is strictly localized, usually in the right lower quadrant of the abdomen; it is continuous, never colicky, and it is intensified on palpation or by any sudden movement. The mechanism of this later pain cannot be attributed to a viscerosensory reflex, for the median development of the appendix and mid-gut would postulate a bilateral innervation and bilateral pain. Moreover, on the reflex theory the innervation would be quite independent of the final position of the appendix, which migrates to the right side at a late period in development, yet it is a common experience that the localized pain of appendicitis begins directly over the diseased organ, and indeed is a reliable guide to its situation. This would seem to indicate that the pain is not dependent upon any reflex mechanism, but is due to irritation of sensitive structures related to the appendix.

It is well known that the anterior parietal peritoneum is exquisitely sensitive, and in many cases the local pain of appendicitis is due to irritation of this membrane. The parietal peritoneum lateral to the cæcum is also very sensitive, the posterior peritoneum less so. Kinsella has shown also that the meso-appendix, like the mesentery of the small intestine, is extremely sensitive, and such procedures as clamping or ligating the meso-appendix are productive of great pain.

Muscular rigidity, a very constant feature of appendicitis, is to be regarded as a protective mechanism of great value, for it immobilizes the abdominal wall over the site of infection and thus assists in limiting the spread of the disease. According to Mackenzie's hypothesis, the rigidity is due to the radiation of impulses from afferent autonomic filaments to the anterior horn cells of the spinal cord—a visceromotor reflex—but the same considerations hold good that have been referred to in connexion with abdominal pain, and there can be no doubt that, like pain, the rigidity is due directly to irritation of the parietal peritoneum. It is for this reason that the rigidity from a retrocæcal appendix is most severe towards the loin, whilst that from an appendix overhanging the pelvic brim is situated just above the pubis.

Cutaneous hyperæsthesia, a somewhat inconstant sign in acute appendicitis, can also be attributed only to irritation of the parietal peritoneum.

It has been stated that hyperæsthesia is present in appendicitis only when the appendix is unruptured, but this does not accord with general experience. Often it appears as though the degree of hyperæsthesia depends upon the proximity of the appendix to the parietes, the most

intense hyperæsthesia being associated with an appendix that lies immediately under the anterior abdominal wall.

Chronic Appendicular Disease

Chronic appendicular disease may follow an acute or subacute inflammatory attack, in which the infection has subsided and left a diseased organ surrounded by inflammatory adhesions, but the term is now usually restricted to those cases in which the onset of the disease is insidious, and its course not interrupted by exacerbations.

There can be no doubt that in the past the frequency of chronic appendicular disease has been greatly exaggerated, but at the present time there appears to be a danger that surgical opinion will swing to the other extreme.

The difficulty of forming a fair estimate in regard to chronic appendicitis is great, for, on the one hand, it is common to find at autopsy what appears to be a diseased appendix, with obvious fibrosis of its walls and obliteration of its lumen, where there is no history of previous abdominal disease; and, on the other hand, there can be no question that sometimes the symptoms of chronic appendicitis and appendicular dyspepsia are permanently relieved by the removal of an appendix presenting little or no inflammatory change.

The confusion arises in great measure from lack of a clear knowledge of the pathology. An essential point, often not recognized, is that the symptoms and signs are not necessarily due to inflammation in the wall of the appendix, but rather to functional disturbances such as may result from a foreign body, or from adhesions or kinks; and the appendix wall may therefore appear normal even on microscopic examination. Hence the pathologist, judging an appendix by its histology, is in a far less favourable position for a proper appreciation of its harmful potentiality than is the surgeon who examines it at the time of operation. The most striking example of such a disturbance of function in a healthy appendix is seen when lead pellets, such as may be swallowed with shot game, find their way into the healthy appendix and cause symptoms; and there seems little doubt that other non-inflammatory lesions may have similar effects.

Thus it becomes clear that the first hindrance to the proper



FIG. 239. Mucocoele of appendix with diverticula, due to progressive narrowing of the lumen at the proximal end of the appendix by fibrosis. The diverticula project into the meso-appendix and are surrounded by adherent fibro-fatty tissue.

(Department of Surgery, University of Edinburgh.)

understanding of the disease lies in its title. "Chronic appendicitis" signifies an old-standing inflammation—a reaction of the tissues to chronic irritation—and this is a relatively infrequent state; "chronic appendicular disease," on the other hand, which includes also non-inflammatory but symptom-producing lesions, is comparatively common.

Morbid Anatomy. The morbid anatomy may conveniently be described under four headings:—

(1) *True chronic appendicitis.* This condition, a simple inflammatory change, is commonest in children, though it may occur in adults. The appendix becomes thick walled, and the mucous membrane is cedematous and a little congested. The inflammation is most evident in relation to the lymphoid tissue of the wall, and the condition may therefore be aptly compared to chronic tonsillitis.

(2) *Chronic obstructive appendicitis.* This may result from previous acute disease, or from narrowing of the lumen due to any other cause. If the obstruction remains partial, the faecal content becomes inspissated, and the mobility of the appendix is deranged. If the obstruction slowly becomes complete a *mucocele* may develop. Sometimes the mucous membrane herniates through weak places in the muscular coat, particularly at those points on the mesenteric attachment where the vessels enter, and one or more *diverticula* result. Rupture of a mucocele or of a diverticulum into the peritoneal cavity may give rise to a curious mucoid change known as *pseudo-myxoma peritonei*, in which large masses of jelly-like mucoid material collect in the peritoneal cavity. The condition is similar to that following rupture of a pseudo-mucinous cyst of the ovary, and appears to be due to the engrafting of mucus-secreting cells upon adjacent peritoneal surfaces, but such cells can rarely be satisfactorily demonstrated. (See also p. 544.)

(3) *Fibrosis of the appendix.* This is the commonest form of chronic appendicular disease. The appendix wall is thickened at the expense of the lumen, and, from a lax, collapsible structure, it becomes converted into a firm rigid tube. The lumen, normally stellate or X-shaped in cross section, becomes rounded, held open by the unyielding fibrous walls.

There is much difference of opinion regarding both the cause of the fibrosis and its ability to give rise to symptoms. Undoubtedly fibrosis is sometimes due to previous inflammation, but, on the other hand, this cannot always be presumed. In normal subjects the appendix tends to become atrophied after about the age of thirty, and there is little doubt that the fibrosis is often simply part of this process.

The relation of fibrosis of the appendix to symptoms has never been satisfactorily proved. It has been suggested that the contracting fibrous tissue compresses autonomic nerve endings or ganglia, and degenerative changes in these structures have been described, but the evidence is most unconvincing, and it seems probable that fibrous, completely shrivelled appendices should be regarded as harmless. On the other hand, if the fibrosis leads to kinking of the appendix, or to the development of a stricture of its lumen, appendicular obstruction may supervene and cause symptoms.

(4) *Foreign bodies in the appendix.* A foreign body may be present

in a healthy appendix, or in one which from some kinking or partial obstruction is unable to empty itself completely. The foreign body is usually a faecal concretion, but a great variety of other objects have occasionally been found. Reference has already been made to the occurrence of threadworms and occasionally round worms, and in children the former are not infrequently the cause of mild appendicular discomfort. A striking instance of a symptom-producing foreign body, to which reference has already been made, is the lead pellet. Occasionally as many as forty or fifty pellets may collect in the appendix, eventually becoming coated with inspissated faecal matter and either faceted like gall stones or glued in a single mass. They give rise to symptoms either in virtue of their weight, or by initiating intermittent appendicular spasms with pain referred to the umbilical region.

Effects of Chronic Appendicular Disease. In the past, innumerable symptoms and signs, from melancholia to habitual constipation, have been attributed to appendicular disease, and the promiscuity of the complaints is largely responsible for the agnosticism in regard to chronic appendicitis at the present day. The greatest difficulty lies in differentiating disturbances of adjacent viscera, the caecum, kidney and female pelvic organs, and visceroptosis in particular is responsible for many of the symptoms that may be attributed to the appendix.

It appears most rational to classify the effects as local, general and reflex. The local effects are often not well defined, and are often limited to tenderness on firm pressure, sometimes with slightly increased tonus of the right rectus muscle. Spontaneous local pain is uncommon, but mild colicky pain, generalized over the lower abdomen, may occur if the appendix is obstructed or if it contains a foreign body. The general effects are extremely ill defined, for they are due to the absorption of toxic products and are in no way specific. Loss of appetite, headache, and a coated tongue are the most striking features, but not infrequently the principal complaint is merely loss of energy and strength. The reflex effects are of particular interest, for they may mimic other intra-abdominal diseases and thus confuse the diagnosis. As Trotter has pointed out, the delicately balanced coordination of intestinal movements is very readily upset by any reflex process. Disturbance of this mechanism is first manifest in interference with the smooth passage of gas along the intestine and in the sensations of flatulence. Later defective coordination leads to constipation or, less commonly, to looseness of the bowels. The motility and the secretory activity of the stomach also depend upon a delicately adjusted mechanism, which is easily disturbed by appendicular disease. Nausea and bilious vomiting, with heartburn, and acidity make up the clinical syndrome of appendicular dyspepsia, and epigastric discomfort occurs and may closely simulate the pain of peptic ulcer or cholecystitis.

TUMOURS OF THE APPENDIX

Two distinct types of tumours occur in the appendix. the one—**adeno-carcinoma**—extremely rare, the other—**carcinoid tumour**—quite common.

Adeno-carcinoma. Adeno-carcinoma is a rare tumour. It occurs in elderly subjects and resembles adeno-carcinoma in other parts of the bowel both in appearance and behaviour. It is composed of columnar cells derived from the mucous membrane, arranged in acinar formation and supported by a connective tissue stroma. It tends to ulcerate at an early age and to infiltrate neighbouring parts and may metastasize to the liver or to more distant sites.

Carcinoid Tumour. A carcinoid tumour is considerably more common and is said to constitute 0.4% of all appendiceal lesions found at operation. It occurs commonly in young persons, especially between the ages of twenty and thirty years, and is of particular interest in several respects, for although locally invasive and possessed of certain



FIG. 240. Carcinoid tumour of the appendix. $\times 110$. The tumour is composed of spheroidal cells arranged in alveoli. Note the close relation of the cells to the muscle fibres at the lower part of the section.

(Laboratory of Royal College of Physicians of Edinburgh.)

of the microscopic features of carcinoma it does not spread beyond the appendix and only seldom metastasizes.

A carcinoid tumour may occur in any part of the appendix, and is especially common near the tip. Rarely two or three such tumours coexist. The tumour forms a hard, rounded, circumscribed nodule, usually small and rarely exceeding the size of an almond, and it may be recognized on naked-eye examination by its characteristic golden yellow colour.

When small the tumour lies in the substance of the appendix wall, and the mucous membrane over it is intact. When larger it projects under the serous surface and it may press upon and thus occlude the lumen. Occasionally a tumour at the base of the appendix has determined the onset of appendicular obstruction and acute appendicitis. In some cases when the appendix is shrivelled and its lumen obliterated by fibrosis the tumour assumes a central position.

Microscopically a carcinoid tumour is composed of solid masses of epithelial cells arranged in alveoli and supported by a stroma of connective tissue (see Fig. 240). Most of the cells are of spheroidal shape, with a central rounded nucleus and a finely reticulate protoplasm. In places the cells are columnar in shape, and arranged in palisade fashion. Yet again there are sometimes long, bulbous-headed racket-shaped cells, which may be arranged in rosettes. Many of the cells contain cholesterol esters and other lipoids, and these are responsible for the golden yellow colour characteristic of the tumour. Other cells contain fine chromatin granules with a specific affinity for silver stains (argentaffin cells).

The tumour at first lies embedded in the muscle coat, and it spreads between the muscle bundles without destroying them. Often the tumour cells appear to be closely related to the nerve fibres of the myenteric plexus (Auerbach).

Origin of the tumour. Formerly the tumour was regarded as either a true carcinoma of low-grade malignancy or a basal-cell carcinoma derived from the mucous membrane, but these views are now generally discarded, and at present the theories most widely held are those of Ehrlich and of Masson. Ehrlich was impressed by the close relationship of the tumour cells to the nerve fibres of Auerbach's plexus, and on the basis of this observation and of the microscopical appearance of the cells he regarded the tumour as a neurocytoma originating in the autonomic nerves. Masson has examined the microscopic characters of the cells in great detail, and he has brought evidence to show that they are derived from the so-called Kulchitsky cells of the crypts of Lieberkühn. These cells are believed to be of entodermal origin, but to be related intimately with the autonomic nervous system, and they are characterized by a specific affinity for certain silver stains. On the basis of his observations Masson has called the tumours *argentaffin tumours*, and has classed them correspondingly with tumours of the adrenal medulla and of the paraganglia of the autonomic nervous system.

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CHAPTER XXVI

DISEASES OF THE PERITONEUM

THE peritoneal cavity, with its various recesses and compartments, forms a potential space of vast dimension. The lining membrane is composed of a single layer of flat endothelial cells supported by delicate areolar tissue. It forms a smooth glistening surface, admirably adapted to subserve its principal function of facilitating the physiological movements of the gut and viscera.

The intimate relation of the peritoneum to the alimentary tract and pelvic organs renders it peculiarly liable to implication in diseases originating in these parts, but fortunately, in addition to its physiological rôle as a gliding surface, the peritoneum has valuable properties for combating even gross infection. Indeed the peritoneum can deal effectively with massive doses of organisms which in most other tissues would spread widely. From the time of the advent of organisms to the gut of the new-born child the peritoneum is continually subject to small bacterial assaults, and thus acquires an increasing natural resistance. By contrast the pleura and pericardium, although derived from the same primitive body cavity, are much less resistant to infection.

Absorption from the Peritoneal Cavity. Owing to its vast surface and the specialized character of its epithelium, the peritoneum has an immense absorptive power. In health this property is mainly protective, for it ensures that small amounts of deleterious substances are rapidly disposed of; but in peritonitis the rapid absorption of toxic products constitutes one of the gravest dangers of the disease.

It is now established that the mode of absorption of fluids and soluble toxins differs from that of particles such as bacteria. When fluid is injected into the peritoneal cavity comparatively little reaches the thoracic duct, and the greater part passes directly into the blood stream by a simple physical process of dialysation through the endothelial lining membrane. The rate of absorption is extremely rapid, and in some respects the peritoneum is a speedier avenue for the administration of fluids than the subcutaneous tissue.

Absorption takes place equally readily and rapidly from all parts of the peritoneal cavity. Accordingly the design of the semi-sitting (Fowler's) position, namely, to divert the toxic products to a "non-absorptive" region of the peritoneal cavity, can no longer be upheld. It seems probable that the semi-sitting position owes its undoubted value principally to the greater freedom of respiratory movement which it allows. It is valuable also in that it facilitates localization of exudates in accessible positions such as the pelvis, and diminishes the risk of subphrenic abscess formation.

The routes of removal of particles such as bacteria may be demon-

strated experimentally by the injection of such substances as Indian ink or colloidal silver. After injection into any part of the cavity such pigment is rapidly collected in two clearly defined regions, namely, over the greater omentum and in the subphrenic region. Paterson Brown showed that the route of absorption from these regions varies in different animals. In rabbits the pigment rapidly reaches the thoracic duct, but in cats and dogs the thoracic duct is hardly affected at all, and the main route of transference is along the lymph vessels of the retrosternal region by which it reaches the cervical veins. There is accumulated evidence that in man the routes are similar and that the thoracic duct plays little part in peritoneal drainage.

Response of the Peritoneum to Infection. When organisms reach the peritoneal cavity they evoke a vigorous reaction. Hyperemia is excited, fluid rapidly exudes from the peritoneal surfaces, and leucocytes and endothelial cells migrate into the cavity, so that the infecting agents are first diluted and dispersed and then subjected to phagocytosis. At first the exudate is turbid and watery, and in some types of infection remains thin, or is sometimes blood-stained, but usually it becomes thick and purulent in the later stages of the disease.

If infection occurs acutely, the peritonitis rapidly becomes widespread; but if the onset is slow the inflammatory process soon becomes delimited and walled off by fibrinous adhesions.

The process by which infection becomes circumscribed affords a remarkable illustration of nature's defensive mechanism, for it depends partly on local inflammatory changes in the peritoneum, partly upon a curious attribute of the omentum, and partly upon simultaneous immobilization of the viscera and abdominal wall. The peritoneal surfaces around the infected region lose their glossy appearance, and adjacent coils of intestine adhere to the abdominal wall; the omentum is disposed around the focus of disease; intestinal peristalsis is inhibited reflexly or by toxic paralysis of the muscular coats; the movements of the abdominal wall are reduced by reflex muscular spasm; and thus by this mechanism of immobilization the defensive processes are perfected. The most remarkable part of this process is the striking protective behaviour of the omentum, which has earned for itself the title "the policeman of the abdomen." No matter where the focus of infection lies, whether in the gall-bladder or the uterine tube, the omentum, if given time, will become adherent to it and envelop it. There is, of course, no purposeful movement on the part of the omentum, and the whole process appears to depend on the abdominal movements, peristaltic and respiratory, and also on the fact that the inflamed peritoneum favours cohesion.

Peritoneal Watersheds. The irregular contour of the posterior abdominal wall and the complicated arrangement of the peritoneal folds create barriers which limit the diffusion of septic fluids and promote the localization of peritoneal infections.

The peritoneal cavity may be regarded as having two compartments, the pelvic portion and the abdomen proper. The latter is naturally subdivided into upper and lower compartments by the transverse colon and its mesocolon. These two compartments communicate in front

of the omentum. The upper compartment lies above and in front of the omentum and mesocolon, and contains three common sources of peritoneal inflammation, the stomach, duodenum and gall-bladder. The lower compartment lies below and behind the omentum and communicates directly with the pelvis. It contains, in addition to small intestine, the commonest source of infection, the appendix.

The lower compartment of the abdominal cavity is divided into right and left portions by the mesentery of the small intestine, which tends to limit the spread of infection from one side to the other.

In the posterior wall of the abdomen the vertebral bodies form a ridge, which, with the root of the mesentery, diverts fluid from the midline towards either flank, where it collects in the paravertebral recesses.

During recumbency fluid above the pelvic brim gravitates towards the diaphragm, whereas fluid below that level falls directly into the pelvis. Hence the upright posture ensures gravitation to the pelvis.

The importance of these topographical features in limiting and directing the spread of effusions is obvious in such acute infections as arise in the appendix. Thus should the appendix lie above the level of the pelvic brim with the patient recumbent, infected fluid will gravitate towards the diaphragm, and pass medial or lateral to the ascending colon according to the relation of the appendix to this viscus. The semi-sitting position will direct the flow towards the pelvis. Should the appendix hang over the pelvic brim an exudate will pass directly to the pelvic floor, whatever may be the position of the patient. In the early stages, peritonitis of appendiceal origin will affect the right flank and the pelvis, while the upper coils of small intestine remain unaffected, but later, if the disease spreads, the infective fluids well out of the pelvis and are directed by the oblique lie of the mesentery mainly to the left side. Hence spreading appendiceal infection may give rise to peritoneal involvement in the left iliac fossa and pain in that region.

ACUTE PERITONITIS

Peritonitis, like any other inflammation, may be the outcome of bacterial or non-bacterial irritation. Non-bacterial peritonitis occurs when a sterile foreign substance or an effusion of blood is present in the cavity, and occasionally when a cyst ruptures or when sterile bile is extravasated; but these are rare occurrences, whereas peritonitis from infection is common. Moreover, even the rare non-bacterial type does not usually remain aseptic, for the effusion is very liable to secondary infection, especially with organisms of mild pathogenic properties, such as *staphylococcus albus*.

In the majority of cases acute peritonitis is due to infection from some local focus in the abdomen, especially in the alimentary tract, its appendages or the pelvic organs, but occasionally it is a *hæmatogenous* infection, as in septicæmic conditions. Rarely, as in gonococcal peritonitis, it seems to follow direct infection from the exterior, by way of the uterine tubes.

The common causes of acute peritonitis include (1) perforation of

hollow organs, (2) simple inflammations, and (3) strangulation of bowel. Appendicitis heads the list, and after it come salpingitis, perforations of peptic ulcers, cholecystitis, volvulus, etc.

The extent and gravity of acute peritonitis depend upon many circumstances, and clinically no two cases are similar. The virulence of the infection varies greatly. In gonococcal salpingitis or in cholecystitis it is almost always mild, in appendicitis it may be mild or severe, and in perforative lesions and diseases of the colon it is often fulminating. Staphylococci and non-hæmolytic streptococci are often relatively innocuous, and coliform bacilli vary greatly, whereas hæmolytic streptococci and anaerobes are often intensely virulent.

Bacteriology of Acute Peritonitis. As may be expected from the diversity of origin of the disease the bacterial flora of peritonitis is very varied. *Bacillus coli* is undoubtedly the commonest, but hæmolytic streptococci are not infrequent, and non-hæmolytic streptococci, gonococci, pneumococci, staphylococci or anaerobes occur. In rare cases acute tuberculous peritonitis has been observed. Sometimes there is a mixed infection, especially of coliform bacilli and streptococci. This is demonstrable in direct films made from the peritoneal exudate, but is apt to be missed on culture, for the more delicate streptococci are liable to be outgrown by coliform bacilli.

Acute Localized Peritonitis. Unless infection of the peritoneum be very acute it remains localized, and soon becomes circumscribed by adhesion of intestinal loops to the parietes. This often ends in resolution, and the inflammatory products are absorbed, but if the infection is more severe a local abscess may form, either in the neighbourhood of the original infection, *e.g.*, around the appendix, or at some more distant site, such as the pelvic cavity or the subphrenic space. A *pelvic abscess* may follow appendicitis, salpingitis or other inflammation. The abscess may remain small and eventually undergo resolution, or it may enlarge and perforate into the rectum or other hollow viscus, or even point externally. If unrelieved, the abscess may burst into the general peritoneal cavity.

Acute Diffuse Peritonitis. "Generalized" peritonitis is rare, because death usually occurs before this stage is reached. It is more accurate, therefore, to use the term "diffuse peritonitis," which indicates a non-circumscribed, and spreading, but not universal, inflammation.

The pathology of peritonitis is essentially the same as inflammation in any other tissue, but its progress is greatly modified and aggravated by two factors peculiar to the situation, namely (1) the vast extent of the absorptive area, which leads to rapid dispersion of toxins, and (2) secondary intestinal paralysis, which brings the danger of obstruction.

The inflamed peritoneal surfaces become injected, engorged and of deep red colour, and the natural lustre is replaced by a dull, matt, velvety appearance. The intestine is dilated and paralysed, and adjacent loops adhere. Often there are masses of thick yellow lymph on the surfaces and in the fluid.

The exudate varies with the type of infection and with its stage. In *B. coli* peritonitis the exudate is usually purulent, yellow or yellowish-

white, and with a characteristic fetor; in streptococcal infections it is often thin, turbid, or sanguineous; in mixed infections, especially when derived from the colon, it may have a stercoraceous appearance and smell, and gas may be present. After perforation of a gastric or of a duodenal ulcer the exudate may be mixed with gastric contents or bile; and in strangulation it may be deeply stained with blood.

Wilkie has shown that the microscopic appearance of a diffuse exudate, in addition to demonstrating the type of organisms, may afford a valuable indication of the progress of the infection and consequently of the prospects of recovery. At an early stage the fluid naturally contains many organisms as well as pus cells, but after the peritonitis has progressed for several hours the altered appearances suggest its extent and the degree of reaction. In a virulent infection the fluid still contains many free organisms, and the pus cells show signs of degeneration. If the resistance is good, however, most of the organisms will have undergone phagocytosis. In later stages of a resolving peritonitis the striking feature is the presence of many large mononuclear or endothelial cells, which appear to act as scavengers both of bacteria and of damaged polymorphs.

The stage of resolution of peritonitis affords evidence of the remarkable properties of the endothelial lining membrane of the peritoneum. Fluid exudate is rapidly absorbed, and even large masses of fibrinous exudate quickly disappear. In most cases adhesions are absorbed and in a few months there may be little sign that there has been peritonitis. In other cases, however, such complete resolution does not take place, and widespread adhesions or long fibrous bands remain, often to cause later trouble from intestinal obstruction. There seems to be an individual idiosyncrasy towards the formation of adhesions.

Cause of Death in Peritonitis. The cause of death in peritonitis is not fully understood. Septicæmia rarely plays a part, but it is not certain whether the profound toxæmia that is so characteristic a feature is due wholly to absorption of toxins from the peritoneal cavity or to secondary intestinal obstruction (*see* also p. 490). The question is of great importance from the therapeutic point of view, for the treatment of peritonitis necessitates rest, whereas the treatment of partial intestinal obstruction demands maintenance of peristalsis.

Bonney and Sampson Handley supported the view that intestinal obstruction is an important factor. It is supposed that in diffuse peritonitis the whole intestine is paralysed—paralytic ileus—but Handley believes that this is unlikely and that only those parts of the gut lying in the pelvis are, in the first instance, involved. He pointed out that at the time of death peritonitis rarely reaches the level of the umbilicus and that the jejunum is comparatively unaffected; whereas the ileum, which lies bathed in pus in the pelvis, is completely flaccid. According to this view, there is often a double obstruction—ileus duplex—namely, in the ileum and in the pelvic colon; and the rational treatment consists in diverting the jejunal contents into the colon, and in draining the large gut at the cæcum.

Experience has not confirmed these views. In diffuse peritonitis there is, undoubtedly, a toxic paralysis of the intestinal muscle, but it

seems probable that its effect is mainly protective, in that it inhibits intestinal movements and circumscribes the infection. It seems probable that the essential factor in death from peritonitis is the absorption of poisonous products from the infective area, and that the obstruction factor is of somewhat secondary importance.

Paralytic ileus must be clearly distinguished from another quite distinct complication of peritonitis, namely, a mechanical obstruction due to plastic adhesions between intestinal coils. Such adhesions are often formed at a stage when the toxæmia of peritonitis has been overcome, and thus the patient after recovering from peritonitis may be a victim of obstruction.

GNOCOCCAL PERITONITIS

This disease is limited to females. It usually arises within a short time of the primary infection, and is secondary to disease of the Fallopian tubes. In most cases, no doubt, the organisms gain access to the peritoneal cavity by way of the abdominal ostium: in other cases where this orifice is closed by adhesions or fibrosis it is presumed that infection has leaked through the diseased wall of the tube. Though commonest in adult women, gonococcal peritonitis may affect young girls, following vulvo-vaginitis.

In most cases the infection is limited to the pelvis, and is most intense around the tubes and ovaries, but occasionally it extends beyond these confines and becomes more or less diffuse. At first there is often an acute phase, but the infection is never virulent, and in the course of a few days it tends to subside spontaneously, but it nearly always leaves behind a low-grade inflammatory process, which may persist for a long period or never completely resolve. In the early stages there is an effusion of fluid, at first thin and serous, later purulent, and the surfaces of the pelvic peritoneum are congested and covered with fibrinous deposits. The demonstration of gonococci in the fluid is always difficult, and by ordinary cultural methods the fluid usually proves sterile. In some cases there is a mixed infection, and the presence of gonococci is masked by other organisms, of which the most frequent is a streptococcus.

In the later stages of gonococcal peritonitis the most striking pathological feature is the presence of numerous adhesions, and this is the principal factor in prolonging the clinical manifestations of the disease. Thick bands or more delicate "cobweb" adhesions bind the tubes and ovaries to adjacent surfaces, and often form a tough matted mass in which may be involved the appendix, the pelvic colon, and the dependent coils of the ileum. The disease is usually bilateral, though often more severe on one side than the other.

PNEUMOCOCCAL PERITONITIS

This form of peritonitis occurs principally in children. Two varieties are recognized according as the disease appears to arise primarily or is secondary to pneumococcal affection elsewhere.

Primary Pneumococcal Peritonitis. This is almost restricted to

female children. The disease occurs with greatest frequency between the ages of three and seven years. It has been suggested that the infection reaches the peritoneum from the genital tract. Pneumococcal peritonitis is rare in well-cared-for children, but is apt to attack those living in squalid surroundings, in whom the vulva and vagina may become contaminated with dirt and infective material. In smears taken from the vagina of neglected children pneumococci may be demonstrated, and in many cases of pneumococcal peritonitis the organism may be cultivated from the vaginal secretion, which, in a few cases, is purulent. The fact that the organism from the vagina is of the same type as that in the peritoneum has suggested that the infection is an ascending one. After the age of seven or eight years the vagina secretion becomes acid and presumably inhibits infection.

More recent work, however, suggests that pneumococcal peritonitis is usually the result of infection by blood-borne organisms. In some cases the peritoneal infection is merely part of a pneumococcal septicæmia; in other cases the peritonitis assumes the rôle of a fixation abscess and may therefore be regarded as a beneficent reaction.

In the early stages of pneumococcal peritonitis there is an oily or sticky exudate in the pelvis, and the peritoneum is very congested. Later the exudate becomes watery or slightly blood-stained, and eventually purulent, and there may be flakes of fibrinous lymph, which adhere to the peritoneum or to the intestine. The fimbriæ of the uterine tubes show a fiery hyperæmia, and pus, containing pneumococci, can be expressed from their lumen. The interior of the tubes presents the signs of catarrhal inflammation. In some, especially in older children, the process is more chronic, and the infection becomes localized by adhesion of the intestines and the omentum, so that a large pelvic abscess results. The process may be sufficiently chronic to create confusion with tuberculous peritonitis or sufficiently acute to simulate acute appendicitis. The abscess may rupture at the umbilicus or into the bladder or rectum.

As primary pneumococcal peritonitis begins in the pelvis, irritation of the pelvic viscera, especially the colon and bladder, is the outstanding sign of the disease, and therefore the child suffers from frequent or painful micturition as well as from tenesmus and diarrhœa with much mucus or even blood in the stools. After peritonitis has persisted for a time the systemic effects of the pneumococcal infection become manifest, and the pulse-rate and respiration become rapid and toxæmia is severe. There is usually a considerable leucocytosis, and in blood cultures the pneumococcus can often be found. In the later stages the systemic illness may completely overshadow the peritonitis. In young children the disease runs a rapid course and generally ends fatally; but in older children recovery may occur.

Secondary Pneumococcal Peritonitis. This occurs as a complication of some other pneumococcal lesion, such as pneumonia or empyema or, occasionally, otitis media. Either sex may be affected, and though the disease is commoner in children it may occur in adults. Infection reaches the peritoneum by the blood stream and at the same time there may be other secondary pneumococcal manifestations, such as peri-

carditis and meningitis. Any part of the peritoneal cavity may be involved. Sometimes the peritonitis is very localized, in others it is widely diffused. The exudate may be serous or purulent. If recovery occurs a localized abscess may form.

Similar to secondary pneumococcal peritonitis is the streptococcal peritonitis that is sometimes seen in childhood. The organism is usually of a hæmolytic variety, and its source may be the nasopharynx or the lower respiratory tract. A few cases have been traced to the genital tract in females. The sexes are affected about equally.

STREPTOCOCCAL PERITONITIS

The streptococci in peritonitis are frequently hæmolytic organisms of great virulence, and streptococcal peritonitis is consequently a grave infection.

It may arise in the course of scarlet fever, but is most common as a complication of puerperal endometritis. From the uterus the organisms gain access to the peritoneum along the uterine tubes, or directly through the uterine wall, or by way of infected thrombi in the large uterine veins. The disease may remain localized to the pelvis, but often spreads diffusely over the greater part of the abdomen. The fluid exudate is thin, watery and often sanguineous, and it contains few pus cells but immense numbers of organisms. A striking feature is the great dilatation of the gut, and the laxity of the abdominal wall after childbirth allows the distension to proceed to an extreme degree, so that the abdominal enlargement even exceeds that of pregnancy.

Post-operative peritonitis also is often due to streptococci, though coliform bacilli may be present as well. The condition may arise from soiling of the peritoneum at operation or from some subsequent cause, for example, from leakage at an anastomosis, but in some cases the source is not discoverable. In such circumstances a hæmatogenous infection from distant septic foci may be incriminated, but there is good reason to suppose that most frequently there has been contamination at the time of operation, from faulty technique.

Post-operative peritonitis is remarkable in that many of the usual signs of peritonitis are absent. There may be no pain, no abdominal rigidity and no rise of temperature, but only gradually increasing distension and a rising pulse rate.

TUBERCULOUS PERITONITIS

Tuberculous peritonitis may affect persons of either sex and at any age, but it is commonest in childhood and early adult life. In the majority of cases infection is derived by direct extension from some primary focus within the abdomen, such as a tuberculous ulcer of the small intestine, mesenteric lymph glands, or a tuberculous uterine tube. Sometimes infection is blood-borne from foci elsewhere or there may be active tuberculosis in the lung and pleura or elsewhere.

Acute Tuberculous Peritonitis. Acute tuberculous peritonitis may occur alone or as part of a generalized miliary infection. The peritoneum becomes covered by numerous minute greyish tubercles and

a fluid exudate usually of a serous character accumulates. (Since the spleen is enlarged and a lymphocytosis is present the condition is liable to be mistaken for typhoid fever, especially as the constitutional disturbances are very similar.

A suppurative type of tuberculous peritonitis occurs, but is distinctly rare. It is seen chiefly in young girls and is usually secondary to disease of the uterine tubes. The peritoneum becomes thickened and œdematous, and covered with jelly-like exudate. Tubercles are scattered over the surfaces, but are often obscured by the thick exudate. The effusion, which may fill the whole abdominal cavity or be restricted to one part of it, is thick, grumous and often of a greenish colour. The disease runs a rapid course, with pronounced emaciation and a hectic temperature. If untreated the abscess may come to the surface, usually at the umbilicus, and a faecal fistula may result.

Chronic Tuberculous Peritonitis. This is considerably more common than the acute form, and is usually due to spread of infection from the small intestine, from a caseous mesenteric lymph gland, or from the uterine tube. Three distinct clinical types may be recognized: (1) the ascitic type, (2) the dry or adhesive type, and (3) the encysted type.

(1) The ascitic type usually affects children or young adults, but occasionally occurs in later life. The tubercle bacilli, disseminated through the peritoneal cavity from a primary focus, are implanted on the peritoneal surfaces, and innumerable yellowish-grey tubercles develop, varying in size from that of millet seeds to peas or even larger. They may be confluent and give rise to a considerable mass.

A fluid exudate gathers in the peritoneal cavity, and may eventually collect in such large amount that the abdomen becomes distended, the skin stretched and shiny, and the superficial veins dilated. Such a prominent abdomen contrasts strangely with the emaciated thorax and extremities. In boys a patent processus vaginalis may become filled with the fluid, and its peritoneal lining the seat of tubercles. The fluid is serous in character, usually clear and straw coloured, but sometimes turbid or even blood-stained. Microscopically it is found to contain lymphocytes in excess. Bacilli can rarely be demonstrated, even after centrifugalization, but their presence can be proved by guinea-pig inoculation.

(2) The dry type is characterized by formation of extensive adhesions, which bind together adjacent viscera, especially coils of ileum. This form is usually limited to one part of the abdomen, and is especially marked around the primary focus of infection, for example, a caseous mesenteric gland. Intestine coils adhere and these, together with the thickened mesentery and omentum, may sometimes be felt as an irregular doughy swelling. Caseation within the mass is common. Sometimes the omentum is infiltrated with tubercles and becomes bunched up into a firm cylindrical mass, which may be felt lying across the upper abdomen. Often the parietal peritoneum is greatly thickened and œdematous, and in some cases so extensive are the adhesions of the viscera to the abdominal wall that exploration is impossible. Fistulae are common in this form of disease, either between various portions of the intestinal tract or to the exterior. Another complication of some

frequency is intestinal obstruction which, however, seldom culminates acutely. Even if the condition resolves there will still remain a grave risk of obstruction or even strangulation from adhesions.

(3) The encysted form is rare. It may be regarded as a combination of the other two types, for there is a localized collection of fluid in a region bounded by fibrous adhesions. The fluid collection is often situated in the pelvis, and in women it is liable to be mistaken for an ovarian cyst. Since the fluid is walled off by adhesions of intestinal coils the swelling may be tympanitic on percussion. Apart from the localized collection the remainder of the peritoneal cavity may be free from disease.

BILIARY PERITONITIS

Intraperitoneal extravasation of bile may follow injury to the biliary tract, it may result from perforation of the gall-bladder in acute cholecystitis, or it may occur without demonstrable cause. Its effects depend principally upon the presence or absence of infection, for in man, unlike certain laboratory animals, a sterile effusion of bile leads to remarkably little disturbance, probably because human bile contains comparatively little of the toxic bile salt, sodium tauracholate.

(1) Biliary extravasation due to trauma is generally a sequel to a severe crush injury rupturing the bile ducts close to the porta hepatis. Bile accumulates in the peritoneal cavity, sometimes painlessly, and reabsorption of its pigment leads to jaundice. In some cases a remarkably large amount of bile escapes. In the case reported by Barlow in 1844, 32 quarts of pure bile were evacuated by paracentesis during three months, with ultimate survival.

(2) Biliary extravasation due to cholecystitis occurs mainly in fulminating infections in elderly persons. The perforation may be a large one, or so small as to be barely visible, as in Leriche's case, in which the bile filtered through an apparently intact gall-bladder wall, "a veritable biliary dew." The fluid is highly infective and leads to diffuse peritonitis, which in nearly 50% of cases proves fatal.

(3) Biliary extravasation without obvious cause, the so-called "perforationless biliary peritonitis," has only recently been recognized. The extravasation occurs suddenly, with symptoms suggesting a gastric or duodenal perforation. There is free bile in the peritoneal cavity, and the extraperitoneal tissues round the common bile duct are discoloured or almost necrotic, but there is no evident perforation and neither the site nor the cause of the leakage is apparent. It seems likely that in most cases there has been a minute perforation of the common duct which has healed spontaneously. The perforation has been attributed to rupture of a glandular crypt in the duct wall, to ulcerative cholangitis, or even to erosion of the mucosa of the duct by reflux of pancreatic juice from the biliary ampulla.

SUBPHRENIC ABSCESS

Subphrenic abscess is a sequel of infection elsewhere in the abdomen. The toxæmia to which it gives rise and the inaccessibility of the infective process account for the anxiety with which it is regarded.

In the majority of cases subphrenic abscess follows an intra-abdominal suppurative lesion, and of these fully 50% are attributable to gastric or duodenal affections and to appendicitis, the remainder to diseases of the liver and bile passages, or of the intestines, kidneys or pelvic organs. Occasionally a subphrenic abscess follows infection above the diaphragm, such as empyema, but it is remarkable that transdiaphragmatic spread is much less common from thorax to abdomen than in the reverse direction. Rarely a subphrenic abscess follows hæmatogenous infection from a distant source.

Anatomically, the subphrenic region is divided into six potential spaces by the cruciform arrangement of the peritoneal ligaments of the liver, and Barnard has emphasized that infections are often limited to one of them, and that the particular space infected depends upon the site of the original disease and the avenue of infection. Of the six potential spaces there are three on each side of the mesial plane, two intra- and one extra-peritoneal.

The right anterior intraperitoneal space is the upward prolongation of the main peritoneal cavity in front of the liver, and it occupies a position under the right vault of the diaphragm. The right posterior intraperitoneal space is subhepatic rather than subphrenic, and is usually described as the subhepatic or right kidney pouch. The right extraperitoneal space corresponds to the "bare area" of the liver, between the layers of the coronary ligament.

On the left side the anterior intraperitoneal space occupies the left vault of the diaphragm, in front of and above the stomach; the posterior intraperitoneal space is merely the upper part of the omental bursa, and the extraperitoneal space does not exist in health, but appears where pus, collecting around the upper extremity of the left kidney, separates the peritoneum from the diaphragm.

The avenue by which infection reaches one of these spaces varies in different cases. From a perforated duodenal ulcer infected fluid is diverted to the right of the mesial plane by the projection formed by the vertebral column, and under the influence of gravity and the aspiration action of the diaphragm, the fluid usually reaches the subhepatic or right kidney pouch (right posterior intraperitoneal space). A gastric ulcer on the anterior aspect of the smaller curvature readily infects the left anterior compartment, and one on the posterior aspect leaks directly into the omental bursa (left posterior intraperitoneal space). Appendicitis usually leads to abscess formation in one of the compartments on the right side; the intraperitoneal spaces are liable to be involved as a result of a fairly diffuse peritonitis, and the extra-peritoneal space may be infected by cellulitis spreading along the retro-cæcal connective tissues.

It is important to recognize that a subphrenic abscess is not always a single large cavity, and that there may be several pockets communicating by narrow channels or separated by soft adhesions. The pus is thick, and often contains necrotic areolar tissue. Gas may be present, either from the action of gas-producing organisms or as a result of leakage from a hollow viscus such as the stomach. When the abscess is situated towards the front it may displace the liver downwards

and approach the skin surface below the costal margin, but often the liver is extensively fixed by adhesions, and the abscess then elevates the diaphragm. Elevation and fixation of the diaphragm indeed constitute a significant radiological evidence of subphrenic abscess.

The infecting organism is most commonly *B. coli*, often mixed with streptococci. Not infrequently anaerobes are present.

A subphrenic abscess may undergo resolution or become chronic, but much more often it progresses, and if unrelieved proves fatal. In rare cases it may rupture spontaneously into the lung, pericardium or stomach, or even at the skin surface. Frequently the condition is complicated by basal pleurisy and reactionary effusion. Adhesions bind the elevated diaphragm to the parietes and obliterate the costophrenic sinus, an effusion collects in the pleural cavity, clear or purulent, but in either case often sterile.

TUMOURS OF THE PERITONEUM

Primary tumours of the peritoneum are extremely rare, and indeed it is doubtful if they exist. Many supposed peritoneal tumours have been described, but in most cases there has been no conclusive proof of their peritoneal origin, and it is suspected that many alleged examples are either secondary growths or tumours arising from the extra-peritoneal tissues.

Secondary tumours, on the other hand, are common. In the great majority they are metastatic deposits from primary growths within the abdomen, most often in the stomach, ovaries or large intestine. In other cases they are derived from more distant sources, for example, the breast.

Dissemination of free tumour cells through the cavity of the peritoneum may take place at any time after the growth has reached the serous surface. Once set free tumour cells may be implanted in any part of the cavity and there proliferate. Generally the cells gravitate towards the pelvis and form multiple nodules over the pelvic floor, and sometimes one may even grow to such a size as to be palpable *per rectum*; such a mass in the pelvis may simulate a primary tumour growing from the colon or pelvic organs, especially if the actual primary lesion is relatively symptomless. Often the malignant cells become implanted on the surface of one or both ovaries, and there set up secondary growths, which may attain considerable size. The so-called Krukenberg tumour arises in this fashion. It is a secondary carcinoma derived from a primary growth in the stomach, colon or other organ, and its special feature is the presence of globules of clear mucoid material within the cells with displacement of the nucleus creating a "signet-ring" appearance. The delayed appearance of gastric or intestinal symptoms renders such tumours very liable to be mistaken for primary growths of the ovary.

In other cases tumour cells floating freely in the peritoneal cavity are caught in the great omentum and proliferate to form a bulky sausage-shaped or apron-like mass readily palpable through the abdominal wall.

One of the most outstanding features of secondary peritoneal involvement is a fluid exudate. A small amount of free fluid may be present before any definite nodules are visible or palpable, and when found at exploratory operation is very suggestive. In the later stages the exudate increases and causes great abdominal distension. The fluid at first may be clear, but is usually blood-stained, and on microscopical examination tumour cells may sometimes be found.

Tumours of the great omentum are almost always secondary to growths in other parts of the abdomen, most often in the stomach, colon, ovary or gall-bladder. Primary sarcoma of the great omentum has been described but is extremely rare.

PSEUDOMYXOMA PERITONEI

This remarkable condition is characterized by masses of gelatinous or mucoid material in the peritoneal cavity, either localized to a particular region or more widely diffused. It occurs as a complication of two entirely different pathological lesions, which superficially appear to possess little in common, namely, cystic tumours of the ovary and mucocoele of the appendix.

(1) **Secondary to Ovarian Tumours.** In most cases the primary lesion is a pseudomucinous cystadenoma, and the peritoneal involvement is usually attributed to the rupture of one of the cysts, with escape of its contents. Pseudomyxoma peritonei may, however, be present where there is no evidence that a cyst has ruptured, and, perhaps more surprising still, it practically never follows accidental rupture of a cyst during operation.

The peritoneal cavity becomes filled with immense quantities of yellowish jelly-like material, which may be scooped out in handfuls. In some cases it is distributed diffusely in homogeneous layers and insinuates itself into all recesses of the cavity, even to the subphrenic space; in others it is circumscribed into large globular masses which lie between intestinal coils or in the pelvis.

It is now acknowledged that the jelly is not colloid or even mucoid, but is almost always composed of pseudomucin, though occasionally true mucin has been present. Its mode of formation is not understood. It has been regarded as a product of the lining cells of the peritoneal cavity, a response to the irritation of the fluid exuded from the primary tumour, but it is difficult to accept this explanation because no comparable reaction on the part of the peritoneum has been witnessed in other diseases. The generally acceptable view is that the pseudomucin is elaborated by the cells of the primary tumour, although such cells are usually scanty and difficult to demonstrate.

Whatever its origin, the exudate causes a form of low-grade inflammatory change in the peritoneum. Fibrin forms and surrounds the jelly material with a delicate capsule, which later is fibrotic. Fine strands of fibrous tissue also traverse the jelly and fix it to the peritoneum, so that at operation the masses are separated with some difficulty, leaving behind stringy, viscid tags. The general peritoneal membrane may also show reactionary changes.

(2) **Secondary to Disease of the Appendix.** A number of cases have been described in which a form of pseudomyxoma peritonci has followed appendiceal disease. In some, a mucoid carcinoma of the appendix has probably been responsible. In others, there has been a mucocele of the appendix or a diverticulum, which has ruptured, disseminating its contents. It is not known whether the gelatinous material is the result of peritoneal irritation, or whether it is the product of mucus-secreting epithelial cells that have been set free from the appendix. There is a further possibility, namely, that the ruptured mucocele remains in free communication with the peritoneal cavity, and thus continuously discharges its secretion.

The effects are very similar to those described in relation to ovarian cysts, but they are more frequently localized to the immediate neighbourhood of the appendix, and only rarely become widespread. The appendix is buried in a gelatinous mass the size of a small orange, or even larger, and the neighbouring peritoneal surfaces show reactionary changes with fibrosis.

TORSION OF THE OMENTUM

Abnormal fixation of the great omentum, as within a hernial sac or from adhesion to a viscus, may provide an obvious axis for rotation. There are cases, however, in which torsion may affect a seemingly healthy omentum. It has occurred most often in adults over thirty years who have recently become obese, but the underlying cause (as applies to torsion of organs in general) remains obscure, although venous engorgement followed by elastic recoil of arteries is a current explanation of its origin. The twist is always clockwise and may be a single rotation or as many as eight. The obvious effect is strangulation, and it is therefore not surprising that the omentum forms a palpable swelling and that a blood-stained effusion develops within the abdomen. The condition is important in that it may simulate appendicitis or cholecystitis.

TUBERCULOSIS OF THE MESENTERIC LYMPH GLANDS

The lymph glands in the abdomen, especially those draining the lower part of the ileum and the first part of the colon, are very commonly the seat of tuberculous infection. Indeed, in Scotland, this is one of the common primary sites of tuberculosis, especially in childhood. General experience suggests that this is not true in other parts of the world. Tuberculosis of the lymph glands in its active form is usually met with in children or young adults and may be responsible for prolonged ill-health and intestinal disturbances. Later, calcification is evidence that at an earlier date the glands have been the site of caseation.

The glands are infected by way of the intestine, and probably milk is the common vehicle by which the tubercle bacillus is conveyed to the body, but in most cases of tuberculous adenitis the intestinal lesion is not obvious. Sometimes only one gland is diseased, but more often several are involved. At first the glands are discrete and firm, and only

a few points of caseation are found in each. Later groups of glands are affected, and an irregular confluent mass results which may be palpable. Such a mass is situated most often in the ilco-cæcal region, but similar masses may be present at higher levels in the mesentery. Sometimes the tuberculous lymph glands soften and form abscesses. Rarely such an abscess ruptures into the peritoneal cavity and may give rise to generalized (though not necessarily fatal) peritonitis.

Tuberculous mesenteric glands tend to heal by fibrosis, and if they are caseous, calcification is the usual result. Localized fibrosis of the mesentery may result in contraction with angulation of the intestine. Adhesion of a loop of intestine to the surface of a tuberculous gland is of fairly frequent occurrence, and may cause kinking by obstruction. In a few instances a mass of tuberculous glands situated at the root of the mesentery of the small intestine has by pressure led to duodenal ileus. Cases have been observed in which the prolonged irritation from calcified glands in the pelvic mesocolon has resulted in megacolon.

In radiographic investigation of lesions outside the intestine, the shadows of calcified tuberculous lymph glands may create confusion. When the shadows are in the region of the kidney or in the line of the ureter they may simulate calculi in these organs. The shadows of calcified glands are often multiple, but in density are not so uniform as those of calculi, and they may alter their position on change of posture.

EMBOLISM AND THROMBOSIS IN THE MESENTERIC BLOOD VESSELS

Occlusion of the mesenteric vessels may involve the arteries or the veins, and in either case it usually leads to infarction of a part of the intestine. Venous occlusion is always due to thrombosis, but arterial occlusion may result from primary thrombosis or from the impaction of an embolus. Rupture of the mesenteric vessels, as may occur from a crush or blast, if not fatal from hæmorrhage, may produce the same effects.

In surgical practice these lesions are rare. They occur usually in subjects past middle life with disease of the circulatory system, and they give rise to a very acute and generally fatal illness. Diagnosis can rarely be made with certainty before the abdomen is opened.

The anatomical peculiarities of the mesenteric circulation require consideration in order that the mechanism of infarction may be understood. The anastomosis between the superior and inferior mesenteric arteries through the ascending branch of the inferior mesenteric and the middle colic artery is a slender one; and if the superior mesenteric artery be suddenly obstructed the inferior mesenteric is insufficient to compensate for its loss, although when occlusion is gradual a collateral circulation may be established. Collateral circulation in the mesentery of the small intestine is very free through the channel of arterial arcades that connect the twelve or more mesenteric vessels, but not through the arteries that pass from the terminal row of arcades to the gut. These arteries are known as the vasa recta. They are short vessels and do not communicate freely

with one another in the mesentery or on the surface of the bowel. Consequently if the vasa recta or the distal arcades are obstructed the vitality of the affected portion of intestine is imperilled. The disposition of the mesenteric veins, though not so uniform, corresponds roughly to that of the arteries.

Arterial Occlusion

Embolism accounts for the majority of cases of arterial occlusion. The inferior mesenteric artery, on account of its small diameter, is rarely entered by an embolus, but the superior artery is of larger calibre and, at its origin, runs almost parallel to the aorta, and is consequently more often occluded. An embolus may originate in the heart or in the aorta, or sometimes from a pyæmic infarct in the lung that has led to septic thrombosis of the pulmonary veins. An embolus from the heart usually takes the form of an organized vegetation from the mitral or, less often from the aortic valve; and it may be detached during the acute stages of endocarditis or at a remoter period. Emboli from the aorta usually arise from organized clot formed on an atheromatous plaque or ulcer.

The superior mesenteric trunk and its larger branches are affected with about equal frequency. The effect of the impaction of the embolus in the main trunk is to cause immediate arrest of the circulation distally. Venous flow in the mesentery ceases; and, as there are no valves in the portal veins, venous engorgement occurs from backflow in the mesenteric veins. Finally, infarction of the intestine occurs. If the embolus is arrested lower down in the mesenteric artery or in one of its larger branches, the collateral vessels are sufficient to maintain the circulation, and would suffice to keep the intestine alive were it not for a secondary thrombosis that usually extends centrifugally from the site of the embolus. If thrombosis reaches the terminal arcades or the vasa recta, infarction is inevitable.

Primary thrombosis in the mesenteric arteries is very rare. It may occur as a result of extension of atheroma of the abdominal aorta, from thrombosis arising in an aneurysm of the superior mesenteric artery, and rarely in association with thromboangitis obliterans. Continental writers have suggested that local arteriosclerosis of the mesenteric arteries may cause thrombosis, and that such narrowing may be a cause of painful intestinal crises in elderly subjects.

Venous Occlusion

Thrombosis in the mesenteric veins may be secondary to obstruction in the portal vein, *e.g.*, from pressure of tumours or in cirrhosis, but it is more often initiated by infective processes in the viscera drained by them.

Appendicitis with suppuration is responsible for most cases. The thrombosis is of an infective character and usually leads to portal pyæmia with abscesses in the liver (*see* p. 571). The pylephlebitis, which is commonest in the ileocolic vein, may be found at operation, but more often it arises as a post-operative complication. Its frequency is less than 1 per 1,000 cases of acute appendicitis.

Simple thrombosis of the veins may, in rare instances, be compensated through collateral vessels, but if the process extends to, or originates in, the peripheral arcades or their tributaries, infarction ensues.

Results of Mesenteric Vascular Occlusion.

The pathological effects of mesenteric vascular occlusion, general and local, are similar to those of strangulation of the intestine and are dependent on the length of bowel involved (*see* p. 492). Hæmorrhagic infarction is the usual result. Whether the obstruction is arterial or venous, the intestine and mesentery become congested, swollen and œdematous. Blood-stained serous fluid is exuded into the peritoneal cavity, and a hæmorrhagic exudate forms in the lumen of the bowel. With the onset of infarction the intestine assumes a dull purple shade, loses its elasticity, and finally becomes gangrenous. The whole small intestine or a small section of it may be involved. The line of demarcation is rarely abrupt. At operation the mesentery is very turgid and friable, and is pulseless over a wide area.

Mesenteric occlusion results in a fulminating abdominal illness with features simulating intestinal obstruction or internal hæmorrhage. The swollen intestine may give rise to a palpable tumour and, if mælena is present, the resemblance to intussusception may be very close.

Operative treatment aims at resecting the devascularized area of intestine and mesentery in the hope of arresting the spreading thrombosis and averting toxic absorption. Success has followed removal of as much as 14 feet of the small intestine.

RETROPERITONEAL AND MESENTERIC CYSTS AND TUMOURS

The majority of cysts and tumours in the retroperitoneal tissues or mesentery arise from the pancreas, kidneys, adrenals, and lymph glands, and are described in their respective chapters. There remain, however, a certain number which arise otherwise, and it is to them that the terms retroperitoneal or mesenteric cysts and tumours are usually applied.

The classification of these conditions is unsatisfactory, for some are simple retention cysts, others are cystic tumours, and yet others are solid tumours. They may arise either between the layers of the mesentery or mesocolon, or in the retroperitoneal areolar tissues. Cysts in the mesentery tend, as they enlarge, to expand the base of the mesentery and eventually to assume a retroperitoneal position, and cysts arising in the retroperitoneal tissue sometimes bulge between the layers of the mesentery.

In general, these retroperitoneal or mesenteric swellings tend to displace the viscera forwards, and they may cause symptoms by pressure on the stomach or intestines. The ureter, being adherent to the posterior parietal peritoneum, may be compressed, and secondary hydronephrosis occur.

Cysts

The following classification of retroperitoneal cysts has been suggested :—

- (1) Traumatic : blood cysts arising from an encapsulated hæmatoma.
- (2) Inflammatory : tuberculous cysts arising from glandular infection.
- (3) Parasitic : hydatid cysts, usually secondary to echinococcus disease of the liver.
- (4) Neoplastic : cysts arising from the degeneration of tumours.
- (5) Dermoid cysts.
- (6) Developmental cysts.

Only the last variety requires further consideration.

Developmental cysts are generally unilocular cysts of simple structure. They lie in the retroperitoneal fatty tissues and are unattached to their surroundings except by areolar tissue. The wall of the cyst is composed of fibrous tissue, and may be thin and almost translucent or very thick. Sometimes there is a lining membrane of columnar, cuboidal or flattened cells. The content is usually a straw-coloured watery fluid of low specific gravity, or it may be blood-stained or chylous. Rarely a multilocular cyst may contain chylous and clear fluids in separate compartments.

The origin of these developmental cysts is not clearly determined and it seems possible that it varies in different examples. The following possible modes of origin have been suggested : (1) lymphatic ; (2) enterogenous ; (3) mesocolic ; (4) urogenital.

Lymphatic cysts, arising from dilatation of lymph vascular networks present in embryonic life, are known to occur in the neck, where they form large thin-walled cavities present at birth (cystic hygroma), and it is possible that some retroperitoneal cysts have a similar origin.

Enterogenous cysts are very rare, and almost always they are situated close to the ileocæcal region. They are believed to originate in congenital diverticula of the small intestine which have lost their continuity with the gut.

Mesocolic cysts are believed to originate from failure of coalescence of the two posterior layers of parietal peritoneum during the third stage of intestinal rotation (*see* p. 485). It is said that the persistence of small islands of peritoneum in such circumstances is responsible for some retroperitoneal cysts containing watery fluid.

Urogenital cysts are probably the commonest form of developmental retroperitoneal cysts. They are derived from rudiments of the mesonephros (Wolfian body) (or from other sequestered portions of the developing genito-urinary system.) Generally they are simple unilocular cavities containing clear watery fluid, but they may be multilocular, and occasionally they resemble the multilocular cystic tumours of the ovary.

Tumours and Cystic Tumours

Sarcoma is the commonest retroperitoneal tumour. It occurs most often in the perinephric region, and principally affects young persons,

Round-cell and spindle-cell varieties are described. In its growth and pathological characters it resembles sarcoma in other parts of the body.

Neuroblastoma (sympathicoblastoma) is not uncommon in young children, in whom it forms a rapidly growing tumour of great malignancy. It arises from the autonomic system, and closely resembles tumours of the adrenal medulla (*see* p. 602).

Ganglioneuroma may arise in the retroperitoneal tissues, or occasionally in the mesentery. It too arises from the autonomic chain, and resembles tumours of similar origin arising from the adrenal medulla and in the mediastinum. Typically, it is a firm rounded tumour which grows slowly to considerable size and remains encapsuled, but occasionally it assumes malignant characters. Microscopically, it contains medullated and non-medullated nerve fibres and numerous ganglion nerve cells.

Lipoma in the retroperitoneal tissues is not uncommon. A *liposarcoma* or mixed fatty tumour has been described, which is characterized by a tendency to infiltrate widely in the retroperitoneal space and even into the vertebral canal. To the naked eye it somewhat resembles a lipoma, but microscopically areas of sarcomatous infiltration are evident. The tumour is very rare.

Teratoma in the retroperitoneal tissues may be solid or cystic and may attain large size and cause pressure symptoms. The tumour is believed to arise from misplaced totipotent cells from the blastomere, or from aberrant sex cells. It occurs principally in women.

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CHAPTER XXVII

DISEASES OF THE GALL-BLADDER, LIVER AND BILE DUCTS

FUNCTIONS OF THE GALL-BLADDER

DESPITE the common observation that cholecystectomy causes little or no digestive disturbance there can be no doubt that the gall-bladder is by no means functionless, and experimental researches suggest that it plays a valuable part in the physiology of the biliary system.

(1) **Concentration of Bile.** As early as the eighteenth century it was recognized that during its stay in the gall-bladder the bile becomes darker and of less watery consistence, as though concentrated, and in recent years clear proof of such a process has been forthcoming from the experimental work of Rous and McMaster. These workers, making use of the fact that in the dog one of the hepatic ducts enters the common bile duct below the level of the gall-bladder, were able to separate by ligature two systems of bile ducts --one connected with the gall-bladder and one draining directly from the liver. By comparing the pigment content of bile derived from each of these systems, the degree of concentration of the bile which had entered the gall-bladder could be estimated. From these experiments it becomes evident that the gall-bladder is able to absorb water from the bile with great rapidity, concentrating the bile within the space of a few hours to a tenth part of its former bulk.

(2) **The Reservoir Function.** The importance of the concentrating property lies especially in the fact that it enables the gall-bladder, in spite of its small size, to act as an adequate reservoir for the bile, storing it in the intervals of digestion and pouring it forth into the duodenum as required. Secretion of bile from the liver is continuous, and from 20 to 30 ozs. are secreted in the course of 24 hours, but by concentration the volume is greatly reduced, and the gall-bladder, whose capacity is about 2 ozs., is thus of adequate size.

(3) **Regulation of Pressure in the Biliary System.** Whenever the sphincter at the lower end of the common duct is contracted the bile is dammed back in the duct system, but by concentration in the gall-bladder and by the elastic expansion of this viscus the potential "back pressure" is countered, and the smaller intrahepatic passages are protected from distension. Evidence of the importance of this function is seen when a functioning gall-bladder is removed, for some temporary dilatation of the whole duct system often then occurs. It is seen again, and in more obvious form, in the early stages of complete obstruction of the common duct, for in this event a functioning gall-bladder, by concentrating the bile and by becoming dilated, delays the increase of intraductal pressure and thus hinders the onset of obstructive jaundice.

(4) **Relation to Cholesterol.** Much has been written on this subject, and directly opposite opinions have been expressed, some authorities believing that cholesterol is absorbed from the bile in the gall-bladder, others that cholesterol is excreted by the vesical mucosa. At present absolute proof is lacking, but there is some evidence in favour of the former view. This will be considered again in relation to cholesterosis of the gall-bladder.

(5) **Discharge of Bile into the Duodenum.** The discharge of bile is governed by a reciprocal nervous mechanism between the sphincter of the common duct and the gall-bladder, a mechanism whereby relaxation of the sphincter coincides with contraction of the gall-bladder, and allows the expulsion of bile, whereas spasm of the sphincter leads to relaxation of the gall-bladder and passive dilatation.

Contraction of the gall-bladder with relaxation of the sphincter of the common duct occurs as a result of the presence of fats in the duodenum, and may follow the intraduodenal administration of various other substances, notably peptone and magnesium sulphate. Ivy and Oldberg have obtained similar results by the injection of an extract of intestinal mucosa resembling *secretin*, to which they give the name *cholecystokinin*. It is possible that a fatty meal may exert its effect on the gall-bladder in a similar way by provoking the formation of some such hormone in the intestinal wall.

A reverse effect—relaxation of the gall-bladder with spasm of the common duct sphincter—is produced by the administration of morphine. This drug, therefore, should be avoided when relaxation of the sphincter is desired, for example in cholangitis or after removal of the gall-bladder.

CHOLECYSTITIS

Cholecystitis is now clearly recognized to be a disease of great frequency, and there is little doubt that in women it is responsible for a large proportion of all chronic digestive disturbances.

Opinion in regard to the relationship between cholecystitis and gall-stones has altered remarkably during recent years. It is now recognized that certain types of gall-stones arise as aseptic formations (pure cholesterol and pure pigment stones), whereas others result from cholecystitis. Aseptic stones may predispose to cholecystitis by simple irritation of the gall-bladder in which they lie, or they may occlude the cystic duct, and thus cause partial or complete stasis of the content.

Two major varieties of cholecystitis are recognized, acute and chronic, and as is customary, the acute variety will be considered first. It must be clearly understood, however, that in the gall-bladder chronic inflammation is considerably more common than acute.

Acute Cholecystitis

Acute cholecystitis, like appendicitis, is beset by a redundant terminology. Catarrhal, suppurative, ulcerative, phlegmonous and gangrenous forms of cholecystitis are described, but it is hardly necessary

to say that these represent degrees or stages in the inflammatory process and not distinct types.

The progress of acute cholecystitis depends partly upon the virulence of the infection, but it is often greatly influenced by previous or coincident obstruction of the cystic duct.

The course of disease in the gall-bladder may be aptly compared to that in the appendix. Both these organs are narrow-mouthed diverticula, and the progress of their diseases is equally liable to be modified by obstruction of their orifices. In the gall-bladder, as in the appendix, obstruction to the outflow may follow or precede infection. The cystic duct may be occluded during the course of acute cholecystitis, the progress of which is thereby aggravated, or it may be occluded as a primary event, *e.g.*, by the simple impaction of a stone, when the resulting stagnation provides a fertile field for bacterial proliferation. Thus it is possible to recognize two processes, acute inflammation and acute obstruction, distinct in origin, sometimes unassociated throughout their course, but very often combined and coadjuvant. This third, combined, type has been described by Morley as "acute obstructive cholecystitis."

(1) **Simple Acute Cholecystitis.** This affection may occur in a gall-bladder which has previously been healthy, but more commonly it supervenes upon existing chronic disease. In man it is almost invariably a bacterial infection, but experimentally it may be produced by the administration of chemical substances such as hypochlorous acid. The organisms present are usually *B. coli* or streptococci, less often *B. typhosus* or *Cl. Welchii*.

Acute cholecystitis may arise in the course of acute infective fevers, as in typhoid fever or even in pneumonia. In these diseases the bile contains large numbers of organisms, and it may be presumed that the gall-bladder is infected by direct implantation. In other instances acute cholecystitis follows infection from some distant site, acute tonsillitis, dental infection, or even mastitis. It is then probably attributable to blood-borne organisms. Often, however, acute cholecystitis arises in healthy subjects, and only perhaps a latent focus in the teeth or in the appendix can be incriminated.

Sometimes the inflammation of acute cholecystitis is at first limited to the mucous membrane—*acute catarrhal cholecystitis*—and it may remain so limited throughout the whole course of the disease, or it may spread widely through the whole wall. Since the infection is usually of low virulence, acute cholecystitis is rarely fulminating, and acute perforation of the gall-bladder is a rare event. In the vast majority of cases an early effect of the disease is to stimulate the formation of adhesions, and the gall-bladder rapidly becomes encased in a thick oedematous mass of omentum, which effectually prevents the spread of infection. Occasionally, however, where the infection is virulent, or when the blood supply to the gall-bladder is impaired, the disease may progress to rapid perforation and widespread peritonitis (*see p. 541*).

(2) **Obstruction of the Cystic Duct.** A stone may be impacted actually within the lumen of the cystic duct, but more commonly the cystic duct is occluded by the indirect pressure of a stone in a

sacculatation at the neck of the gall-bladder (Hartmann's pouch). In other cases, less frequent, obstruction results from other causes—for example, a neoplasm in the ducts or exerting pressure from without, an enlarged lymph gland, simple fibrous stenosis of the duct, or even a foreign body such as a worm or a liver fluke.



FIG. 241. Obstructive cholecystitis. The gall-bladder, thickened and scarred by chronic cholecystitis, has become the seat of an acute infection following the impaction of a cholesterol stone near the cystic duct. The wall of the gall-bladder is acutely congested and its mucous membrane is eroded. At the time of operation the gall-bladder contained muco-pus.

The effects of obstruction of the cystic duct, however it is caused, depend upon the degree and virulence of any present or potential infection. When the process is entirely non-inflammatory, as in a healthy experimental animal when a ligature is placed round the duct, the gall-bladder gradually contracts, and its content becomes inspissated. When a very mild degree of inflammatory change is present, the first effect of the obstruction is to cause secretion of mucus, and the gall-bladder then becomes distended as a *mucocele*, which may remain completely aseptic. When bacterial infection is present, the condition is that known as acute obstructive cholecystitis.

(3) **Acute Obstructive Cholecystitis.** In the great majority of cases of acute cholecystitis seen in surgical practice, an obstructive element is present. The course of the disease is greatly aggravated by the presence of an obstruction, and inflammatory changes proceed

apace, both in the tissues of the wall and in the lumen. The gall-bladder becomes distended and greatly congested, its wall becomes thick, fleshy, and œdematous, the mucous membrane becomes swollen, ulcerated and perhaps gangrenous, and pus is exuded into the lumen—empyema of the gall-bladder.)

If, as usually happens, this acute phase subsides, as the œdema diminishes, the impacted stone loosens or any other obstructing agent is relieved, and the patency of the cystic duct may once again be

restored. Probably the gall-bladder never returns completely to the *status quo ante*, but assumes a state of chronic inflammation, often interrupted later by acute or sub-acute exacerbations.

Although this is the usual course, it sometimes happens that the disease progresses to further complications, and the infection, hitherto practically limited to the gall-bladder, spreads more widely. Gangrene of the gall-bladder wall may occur and lead either to sudden perforation into the general peritoneal cavity or, more commonly, to local abscess formation. As a further event, abscesses may form in the subphrenic space.

Perforation of the gall-bladder may result also from the direct pressure of a stone in the lumen, and in such a case it is usually situated over a stone impacted close to the cystic duct. A fistula may form between the gall-bladder and other structures, especially the common duct or the duodenum, or, rarely, the colon or stomach. Such a fistula may allow the passage of a large stone into the intestines, and this may subsequently give rise to *gall-stone ileus*.

Chronic Cholecystitis

As the diagnosis of early gall-bladder disease has improved it has become increasingly evident that as a rule chronic cholecystitis is not a legacy of acute cholecystitis, but a distinct disease, insidious in onset and slow in progress. It may precede gall-stones or may follow them, as a result of their irritant and obstructive effects.

Naked-eye Appearance. In health the gall-bladder wall is translucent, and transmits the deep blue-green colour of the bile within. One of the earliest signs of disease consists in impairment of this appearance by faint opacity, often first evident near the neck of the gall-bladder (which should therefore always be examined with special care), later extending to the fundus.

Mild cholecystitis is often indicated by three other changes visible to the naked eye. (1) A slight excess of subserous fat; not a thick adipose deposit such as is sometimes present in health, but a delicate layer of a pale yellow colour. (2) Enlargement of the lymph gland draining the gall-bladder, the cystic gland which lies alongside the cystic duct. (3) Subcapsular fibrosis of the liver adjacent to the gall-bladder. No single one of these changes is a positive criterion of cholecystitis, but together they form valuable confirmatory evidence.

The presence of dark tarry bile in the gall-bladder is now recognized to be no proof of cholecystitis. On the contrary, it is an indication of the normal concentrating function.)



FIG. 242. Hour-glass gall-bladder containing stones. The stones are of "pure pigment" type.

In later stages cholecystitis presents no difficulty in recognition. With increasing fibrosis the wall becomes palpably thickened and of pearly white colour, and eventually the thickening may proceed to an extreme degree. The gall-bladder may become dilated, particularly from the pressure of stones, or following impaction of a stone at the cystic duct; it may remain of normal size, or it may contract down to a tough fibrous and almost solid mass. When the gall-bladder is dilated from any cause it often assumes a sigmoid shape, and a curved pouch-like portion bulges downwards, overhangs the cystic duct and often adheres to the common duct. Such adhesions may expose the common duct to injury at operation.

The mucous membrane at first is congested and œdematous; later it may become ulcerated, especially where pressed upon by stones, and eventually extensive scarring may develop, so that the inner surface is trabeculated with criss-cross fibrous bands (*see* Fig. 241). The scarring may lead to stenosis, either at the cystic duct or in the body of the viscus, and in the latter case may lead to some degree of hour-glass deformity. Occasionally in very old-standing disease the wall becomes extensively calcified, so that it may be outlined in a radiogram (*see also* p. 566).

The gall-bladder may contain healthy bile, but often the bile is pale and turbid, and it may contain muco-pus, stones, and the brownish-yellow, cholesterol-rich *débris*, known as biliary mud. The stones may lie loose, or they may fill the whole lumen and lie closely packed in a solid mass. Occasionally they lie in small diverticula in the wall—parietal calculi.

Microscopically, the mucosa at first is often proliferated, and projects in large bulbous or reduplicated folds which contrast strikingly with the delicate villi of the normal organ. Later other signs of chronic inflammation appear, there is an infiltration with small round cells, the muscle coat is atrophied, and fibroblastic and fibrous tissue pervades the whole wall.

Proliferation of the mucosa may lead to the formation of deep clefts lined by epithelium, which penetrate down to, or even through, the muscularis, and when cut obliquely in sections such formations may lead to an appearance like that of invading carcinomatous acini (Rokitansky-Aschoff sinuses). These are to be distinguished from the somewhat similar crypts described by Luschka, which are believed to be aberrant bile ducts traversing the gall-bladder wall.

Occasionally the epithelial proliferation is more extensive, and leads to diffuse or localized thickening of the gall-bladder wall, which is honeycombed by epithelium-lined crypts and glands, some of which may become cystic (cholecystitis glandularis proliferans).

Bacteriology of Cholecystitis. On the assumption that cholecystitis is due to bacterial infection, it would be expected that bacteriological examination of diseased gall-bladders would lead to the isolation of organisms in a large proportion of instances. Early investigations were disappointing in this respect, however, for it was found that cultures from the bile even of grossly diseased gall-bladders were usually sterile. Recently, however, it has been found that a more accurate estimation

of the infection present can be obtained from cultures of the gall-bladder wall.

The results of bacteriological examination are somewhat different in acute and in chronic cholecystitis.

In *chronic cholecystitis* the bile is sterile in a large proportion of instances, for it has a mild inhibiting effect upon the growth of organisms, and moreover is continually being flushed out and replaced. The gall-bladder wall, on the other hand, is often infected, and cultures yield a growth in from 50% to 70% of cases. The organisms most commonly present are streptococci and *B. coli*, usually in pure culture but occasionally mixed. Less often staphylococci, *B. typhosus*, *Cl. Welchii*, or other bacteria are found.

Some evidence favours the view that streptococci play the major rôle in cholecystitis, though often their presence is masked by the prolific growth of secondary invaders. The streptococci are not virulent organisms, but are slow growing, and either non-hæmolytic or of "viridans" type. They usually give the sugar reactions characteristic of *S. salivarius* and *S. faecalis* (enterococcus).

In *acute cholecystitis* the flora is somewhat different. Both gall-bladder wall and bile are usually infected, often giving a profuse growth in culture, and the most common infecting agent is *B. coli*. It has been suggested that this is often a secondary invader whose advent is rendered possible by existing inflammatory changes in the wall or by stagnation of the contents. Streptococci, *Cl. Welchii* and, less often, typhoid bacilli, may be found.

Avenues of Infection. There are four possible avenues by which organisms may reach the gall-bladder.

(1) They may ascend the common duct from the duodenum. This route is generally regarded as unimportant, for even when the gall-bladder is grossly diseased the ducts are usually thin walled and unaffected, and it is general experience that a healthy duct system does not allow retrograde infections, and, moreover, it has been shown that the duodenal content is usually almost sterile.

(2) Organisms may spread to the gall-bladder along lymph channels from the liver. Graham has shown that cholecystitis is very frequently accompanied by a certain degree of hepatitis, and has suggested that the gall-bladder is infected along lymph channels direct from the liver. Although backed by very convincing experimental work this view has not met with general acceptance, and the liver infection is regarded as a secondary event due to primary cholecystitis.

(3) Organisms in the portal blood stream on reaching the liver may escape into the bile and so reach the gall-bladder. It is known that in typhoid fever, in many infections in the portal area, and even in constipation, organisms find their way into the bile, and there is therefore strong *prima facie* support for this view. Further evidence is found in the observations (a) that cholecystitis commonly accompanies disease of the appendix, colon, and other abdominal viscera, and (b) that the common infecting organisms in cholecystitis are coliform bacilli and streptococci of *faecalis* type, both commonly derived from the intestinal tract.

(4) Organisms may reach the gall-bladder directly by the systemic

blood stream, from some distant infective focus. This avenue is suggested by the observation that the gall-bladder wall is frequently infected when the bile remains sterile. It is usually held that infection by way of the systemic blood stream originates in such foci as the teeth, paranasal sinuses or tonsils. Patey and Whitby, however, have shown recently that organisms derived from the intestinal tract may also infect the gall-bladder by this avenue, for the liver is an inefficient bacterial filter and readily permits the access of organisms from the portal to the systemic blood stream.

Ætiology of Cholecystitis. It is generally accepted that cholecystitis in man is due to bacterial infection, though the invariable accuracy of this assumption is by no means proved. According to Rosenow, streptococci are responsible for cholecystitis in a large proportion of cases. He believes that certain strains of these organisms bear an *elective affinity* for the wall of the gall-bladder, but this theory fails to account for certain known facts in regard to cholecystitis. Cholecystitis is rare in young subjects, and is far more common in stout women than thin men, although the incidence of streptococci is presumably fairly uniform. This indicates the importance of some special susceptibility on the part of the patient rather than some special property of the infecting organism. Moreover, in early cholecystitis the gall-bladder wall and bile are commonly sterile, and it would seem likely that in these cases subsequent bacterial infection is secondary to some aseptic predisposing affection. In many cases, undoubtedly, the irritant and obstructive effects of an aseptic cholesterol stone constitute the essential predisposing factor. The incidence of cholecystitis in stout women suggests that in noncalculous cases some disturbance of lipid or cholesterol metabolism may be the basic predisposing factor.

CHOLESTEROSIS OF THE GALL-BLADDER

(Strawberry Gall-bladder)

This disease is by no means uncommon, but until recent years its frequency has not been fully realized. Its characteristic feature lies in the deposition of large amounts of esters of cholesterol and other fat-like substances in the mucous membrane, where they form either multiple small yellow specks like the seeds of a ripe strawberry—*strawberry or fish-scale gall-bladder*—or larger pedunculated masses known as *lipoid polypi*. When the gall-bladder is opened and viewed from its inner aspect, the appearance is striking. In the normal organ the mucosa is raised into delicate ridges or villi. In the “strawberry” condition these ridges instead of being thin and tenuous are stout and swollen, distended by yellow lipid masses. In severe examples the ridges throughout practically the whole gall-bladder may be thus affected, and rarely even the intervening recesses also are invaded. Even when most extensive, however, the change is strictly limited to the gall-bladder itself, and stops short, often in a transverse yellow line, near the commencement of the cystic duct. The cystic duct and the common and hepatic ducts are never affected. Lipoid polypi are localized

deposits of a similar nature, which enlarge and thus become pedunculated. They are usually single, but as many as a dozen may be present, often associated also with some degree of "strawberry" change.

Microscopically, the characteristic changes are confined to the mucous membrane, and the other coats may either be healthy or show merely the signs of chronic inflammation. The ridges or villi of the mucosa, normally delicate tenuous folds, are prominent and swollen with lipid material so that they have been said to resemble balloons, attached to the subjacent walls by delicate stalks. The great mass of the lipid is contained in large cells which lie in the stroma of the mucous membrane, principally in clumps close to the tips of the villi. These lipid-containing cells closely resemble the characteristic cells of subcutaneous xanthoma. The cell nucleus is small and stains deeply, and surrounding it is a very delicate cytoplasmic network in the meshes of which the lipid collects. From their appearance these cells are known as "foamy cells." It is believed that they are of endothelial origin and are engaged in phagocytosis of the cholesterol.

Not infrequently cholesterol is deposited also in the columnar epithelial cells of the mucosa, in the form of large globules near the basal aspect of the cells. When these are stained with Scharlach-R. or similar dyes a striking appearance is produced, as of a scarlet margin to the section.

Pathogenesis. It has often been stated that cholesterosis is a variety of cholecystitis, but this view cannot be accepted, for although the two conditions are often associated, cholesterosis may occur alone, with no trace of inflammatory change. Nor can cholesterosis be due, as has sometimes been suggested, to a mere excess of cholesterol in the



FIG. 243. Cholesterosis of the gall-bladder. There are numerous massive deposits of cholesterol esters in the mucous membrane. Near the fundus there is a small lipid polypus. Note that there are no cholesterol deposits in the cystic and common ducts.

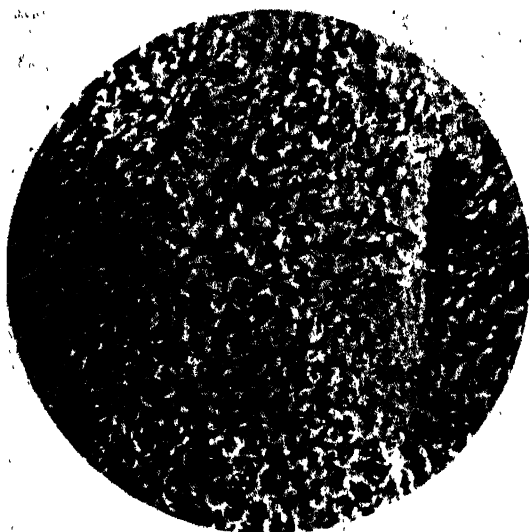


FIG. 244. Cholesterosis of the gall-bladder. Massive deposits of cholesterol esters are seen in the prominent ridges of the mucous membrane.

(Department of Surgery, University of Edinburgh.)

contains much cholesterol, which is either built up by the liver cells or derived from cholesterol in the blood, but it has been found difficult to prove whether the gall-bladder adds further cholesterol or, on the contrary, subtracts some from the bile.

At present there are two main views in regard to the origin of cholesterosis. The first is that the cholesterol is deposited directly from the blood stream, as a result of breakdown of a cholesterol-secreting mechanism in the gall-bladder. The second view, more widely held, is based upon the belief that normally cholesterol is subtracted from the bile in the gall-bladder, but only to a very moderate extent unless the bile-

blood, for the blood-cholesterol index is sometimes normal or even low.

From the strict localization of the cholesterol deposits to the gall-bladder itself, and their entire absence from the ducts, it seems clear that the disease is closely related to the function of the gall-bladder in regard to cholesterol metabolism, but, in spite of much work, our knowledge of this function is not yet complete. It is known that the bile as it leaves the liver con-



FIG. 245. Cholesterosis of the gall-bladder. Paraffin section of a villus of the mucous membrane. The villus is distended by numerous foamy cells, with small nuclei and delicate reticulate protoplasm, in the meshes of which the cholesterol is held.

(Department of Surgery, University of Edinburgh.)

cholesterol concentration is high. In health the absorbed cholesterol is probably combined with other substances which render it "masked" and invisible, and is then transported rapidly into the blood stream. According to this view cholesterosis is thought to result from two processes (1) increased absorption of cholesterol from the bile through the gall-bladder wall, due to a high bile-cholesterol content, and (2) an alteration in the physical or chemical state of the absorbed cholesterol, which renders it visible, prevents its further transport, and leads to its aggregation in large masses.

Relation to Cholecystitis. It is generally believed that cholesterosis is in some way due to cholecystitis, and it has been suggested that the cholesterol deposition results from inflammatory fibrosis and obstruction



FIG. 246. Two villi from a strawberry gall-bladder. (Frozen section stained by Scharlach-Rt.) Cholesterol deposits (left) in the basal parts of the epithelial cells, and (right) in foamy cells in the stroma.

(Department of Surgery, University of Edinburgh.)

of the lymph channels by which the cholesterol is normally carried away. Cholesterosis may occur, however, in an otherwise healthy gall-bladder, although in most examples removed by operations it is accompanied by mild inflammatory change. Moreover, cultures from strawberry gall-bladders are sterile in a large proportion of cases. These facts seem to justify the view that primarily cholesterosis may be an aseptic process. It is possible, however, that cholesterosis renders the gall-bladder liable to infection.

Relation to Gall-stones. Cholesterosis may occur with or without gall-stones. Stones were present in 17 of a series of 85 cases recently examined. It is a striking fact that the stones are commonly of pure cholesterol type. In the series referred to, no fewer than eleven of seventeen stones were of this type, a frequency out of all proportion to their general incidence. The nature of the relationship is considered in the section on gall-stones.

GALL-STONES

It is often stated that there are three principal circumstances that predispose to gall-stone formation: (1) infection of the gall-bladder, (2) stasis of bile, and (3) increase in the cholesterol content of the blood. This statement is to some extent true, but it must be qualified by consideration of the different varieties of stone, for these are very different in appearance and in chemical constitution, and it is consequently entirely irrational to postulate a common cause.

Gall-stones may be classified in three principal types: (a) pure pigment stones, (b) pure cholesterol stones, and (c) stones of mixed



FIG. 247. Cholesterol gall-stones (unripe mulberry type) in a gall-bladder affected by cholesterosis.

(Department of Surgery, University of Edinburgh)

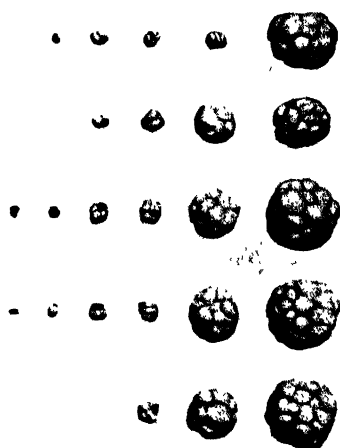


FIG. 248. Gall-stones from a strawberry gall-bladder. The smallest stones are composed of bile pigment. The larger ones consist of lobules of cholesterol deposited upon minute nuclei of pigment. All stages of the process are seen.

(Department of Surgery, University of Edinburgh.)

constitution. Following the work of Aschoff and Bacmeister it seems most rational to regard stones of the first two types as aseptic formations resulting from derangement in the metabolism of pigment and cholesterol respectively, and stones of the third type as resulting from inflammatory processes.

(a) "Pure pigment" Stones (Calcium Bilirubinate). In most countries these stones are uncommon, though they are said to be the most frequent type in Japan. They are multiple, small and dark, and are usually of metallic hardness and smooth. Occasionally they are large and irregular in shape. Some of them arise in the smaller hepatic ducts as "bile thrombi"; others appear to originate in the gall-bladder. They are particularly common in those circumstances in which there is excess of pigment in the bile, as in hæmolytic jaundice. As a rule they

cause little clinical disturbance, for they pass readily along the ducts to the duodenum, but they may occasionally give rise to symptoms, or may form nuclei for cholesterol deposition and thus lead to the formation of larger stones (see Fig. 248).

(b) **"Pure Cholesterol" Stones** (95% to 98% cholesterol) are light yellow in colour, or even pure white, and are rounded or oval, with a smooth or slightly nodular surface. They are usually single (the cholesterol "solitaire" of Meckel v. Hemsbach), or there may be two or three, or even several. Such multiple stones have been compared to unripe yellow mulberries.

Stones of this type are often found associated with cholesterosis, or they may occur in a perfectly healthy gall-bladder, and it appears certain that they arise from metabolic disorders rather than from infection. Cholesterol is normally present in large quantity in the bile, but is held in colloidal solution by the bile salts, and it is not surprising that cholesterol deposition may result either from an excess of cholesterol or from lack of solvent bile salts. Once the cholesterol is thrown out of solution it follows recognized physical laws and tends to aggregate in a single mass, which gradually increases in size over a long period. In a certain proportion of cases the cholesterol is deposited around preformed calculi of "pure pigment" type (see Fig. 248).

The close relationship of pure cholesterol stones to cholesterosis of the gall-bladder is a point of some interest. It has been suggested that the stones originate as "lipoid polypi" which have become loosened from the gall-bladder wall and set free in the bile, but it seems more probable that both stones and cholesterosis result from a common causative factor, an increase in the cholesterol content of the bile.

(c) **Stone of Mixed Composition** (Calcium, Cholesterol, Bilirubin). These are the common gall-stones. They are usually multiple, sometimes numbering several hundreds, and are then always faceted by mutual pressure. Less commonly a single large oval stone is present, perhaps forming an accurate cast of a shrunken gall-bladder, or there may be three or four large barrel-shaped stones. The gall-bladder may contain clear bile, or a brownish-yellow *débris* known as biliary sand or mud. The stones are usually laminated, with a soft friable



FIG. 249. Gall-bladder containing stones. A pure cholesterol stone of aseptic origin, impacted in a sacular dilatation close to the cystic duct, has predisposed to the formation of multiple, faceted, septic stones.

brownish centre rich in cholesterol, which is surrounded by alternate bile-stained and pale laminæ rich in calcium.

These stones are generally believed to result from infection. In many cases culture yields a growth of organisms, but not uncommonly it is found that the stones and the bile or biliary mud are sterile, and even the gall-bladder wall may yield no growth. In these cases it may be supposed that a previous infection has died out.

It is found that "mixed" stones, even when very numerous, are usually all of one size, or in two or three successive "hatchings" or crops, and it may therefore be presumed that the predisposing factors concerned are not constantly present, but are apt to pass off and recur. According to Aschoff, the essential predisposing factor is the occurrence of a mild acute or subacute cholecystitis, with temporary occlusion of the cystic duct and temporary collection of mucus in the gall-bladder. Stone formation occurs subsequently, when the inflammation has subsided and the cystic duct again becomes patent. When fresh bile enters and meets this purulent magna, mutual precipitation occurs, and soft concretions form which later become moulded to stones. Quite commonly, in addition to one or more crops of faceted stones, there is a single rounded stone of larger size, often wedged in the saccular dilatation (Hartmann's pouch) close to the cystic duct (see Fig. 249). This is a combination stone consisting of a central pure cholesterol stone encrusted with secondary mixed deposits. On Aschoff's theory it is to be regarded as a primary aseptic stone which later, by occluding the cystic duct, has given rise to the formation of multiple septic stones.

Rarer Varieties of Stones. Stones composed principally of calcium carbonate are uncommon. They are usually rounded and fairly hard, and are often white and chalk-like in appearance. Occasionally biliverdin may replace the bilirubin of mixed or pure pigment varieties, giving a greenish colour to the stones. Rarely stones may form around foreign bodies, portions of silk or catgut, or even round worms or liver flukes.

Stones in the Bile Ducts. Stones in the bile ducts are usually derived from the gall-bladder, whence they have passed into the common duct either along the cystic duct or by way of a fistulous communication. Occasionally, however, stones may arise primarily in the ducts, either as aseptic formations in the finer bile radicles (small pigment stones) or from the infection and biliary stasis associated with a stricture or obstruction of the common duct. Such stones in the ducts are said to be common in China, owing possibly to the prevalence of liver flukes and other parasites.

Once a stone reaches the common duct its further progress depends upon its size compared to that of the sphincter at the lower end, for the common duct, since it has no muscular coat, is unable to expel the stone actively. The stone may be carried through a lax sphincter by the flow of bile, and probably many small concretions are voided in this way. Larger stones may become impacted immediately above the sphincter, and a stone in this situation may project under the mucosa into the duodenum, and be most readily accessible at operation by the transduodenal route. More commonly the stone does not become fixed

in position, but remains mobile within the duct, and by forming a kind of ball-valve it gives rise to intermittent obstruction with jaundice. Occasionally, however, a stone lies in the common duct for a long period, yet remains symptomless. At first the stone retains its earlier characteristics, and may be rounded, irregular or faceted. After a short sojourn in the duct, however, it receives a coating of soft brownish *débris* and assumes an oval shape, conforming to the long axis of the duct. This putty-like crust may break off when the stone is extracted at operation, and may form a nucleus for further deposits.

In a large proportion of cases the stone not only causes obstruction, partial or complete, but also renders the duct liable to infection. Indeed, cholangitis is rarely due to any cause other than stones. The common duct and all the smaller hepatic radicles become greatly dilated, and the bile becomes mixed with purulent *débris* and with "biliary mud." Cholangitic abscesses may develop and commonly lead to a fatal issue (*see p. 572*).

Recurrence of Stones after Operation. After cholecystostomy stones may recur from a simple recrudescence of the factors originally predisposing to stone formation—aided, no doubt, by the increased infection and scarring of the mucosa which are apt to follow drainage. In some cases a portion of catgut forms the nucleus for new stones. Not infrequently, a "recurrent" stone is one overlooked at a previous operation.

Relation of Gall-stones to Pregnancy. It is a commonplace that gall-stones occur characteristically in the "fair, fat and forty," and that the great majority of sufferers are parous women. In Naunyn's experience 90% of women with gall-stones had borne children, and not infrequently they may date the first onset of the symptoms of stones to the period of one of their pregnancies. It has been generally believed that child-bearing predisposed to stone formation in virtue of the stagnation of the bile, the increased blood cholesterol content, and the greater susceptibility to infections during the later months of pregnancy.

It has been claimed by Gross, however, that the high incidence of gall-stones in the parous is more apparent than real, and is simply due to the circumstance that more than four-fifths of the adult female population is in the married state. Upon what appears to be adequate statistical evidence from the Leeds autopsy records, Gross found that in a large series of gall-stone cases the proportion of married women to single approximated closely to that of the general population. Of 226 females with choledithiasis, 89.8% were married, as compared with 86.6% of a large control series of females with no biliary disease. It would therefore appear that the influence of pregnancy upon gall-stone formation is statistically insignificant. The special susceptibility of females to gall-stones must be due to some factor other than the changes associated with child-bearing.

Gall-stones in Childhood. Gall-stones are uncommon before the age of forty years, and are rare in childhood. There are, however, reported cases occurring in infancy and even in foetal life. Potter has recently collected 226 cases from the literature of gall-bladder disease occurring before the age of fifteen years, including 140 cases in which stones

were present. There were two examples in the fœtus (sixth month and eighth month respectively), twelve in new-born children and twenty-eight in young infants. In some of the older children there was a history of typhoid fever or other infective disease of the abdomen, which may have been the ætiological factor. In others, the records suggest that the stones were of pigment type, and were probably associated with excessive hæmolysis.

Gall-stone Ileus. Impaction of a gall-stone in the intestine is responsible for approximately 1% to 2% of all cases of intestinal obstruction. The site of impaction in the majority of cases is the distal ileum; rarely the stone is arrested in the jejunum, at the ileo-cæcal valve or in the colon.

To obstruct the intestine a gall-stone must necessarily be of considerable size, 2 cm. or more in diameter. Such a stone may reach the intestinal tract *via* the common bile duct (ulcerating through from the lower end of the duct into the duodenum) but this is a rare avenue, and in the majority of cases the stone gains access to the duodenum *via* a cholecyst-duodenal fistula.

Sometimes there is a long history of calculous cholecystitis culminating in an acute attack, and it is evident that the fistula has resulted from rupture of the acutely inflamed gall-bladder into the adherent duodenum. More often there is no antecedent history and it is presumed that a large symptomless stone in the gall-bladder has caused gradual pressure necrosis of the contiguous walls of the two viscera.

After the stone has been extruded, the gall-bladder becomes contracted, forming a small thick-walled cavity, whilst the fistula may also become greatly reduced in size.

The stone on reaching the duodenum may be carried to the ileum and impact within a few hours, or it may remain free in the intestine and acquire a shell of intestinal deposits.

The obstruction which results is at first a partial one, and may remain so during several days; eventually it becomes complete as a result of spasm of the intestine and ulceration and infection of its mucous membrane.

Lack of antecedent history, the variable character of the onset, and, in many, the absence of marked abdominal distension, render diagnosis difficult and are often responsible for dangerous delay in instituting treatment.

CALCIFICATION OF THE GALL-BLADDER

This rare condition is characterized by deposition of calcium in the outer (muscular and subserous) coats of the gall-bladder, either in patchy fashion or throughout the viscus. To outward appearance, the gall-bladder is pale, smooth and shiny, sometimes resembling porcelain. On its inner aspect, the wall is irregular and rough, for the mucous membrane, deprived of its blood supply, generally sloughs.

Calcification of the gall-bladder is almost always a late sequel to calculous cholecystitis. In most cases the gall-bladder is of large size,

is thick-walled, and contains a stone impacted in or close to the cystic duct; and it is obvious that the calcification has supervened upon a chronic obstructive cholecystitis with empyema of the gall-bladder. In addition to the primary obstructing stone the gall-bladder may contain secondary stones composed of calcium carbonate, and also thick gritty *débris*, rich in calcium. In other cases a calcified gall-bladder is of small size, tightly contracted round a large stone or a number of closely-packed faceted stones.

The disease occurs principally in elderly females. It is remarkable that in the majority of cases the symptoms are slight or even absent. The condition may be recognized by the discovery of a painless, mobile, stony hard lump in the right hypochondrium whose outline is obvious radiographically.

VOLVULUS OF THE GALL-BLADDER

A gall-bladder which has an abnormally loose attachment to the liver by a complete mesentery may undergo torsion. Rotation may be clockwise or anti-clockwise, and may be through a full circle. The few cases reported have occurred chiefly in elderly women, and in gall-bladders which in other respects had been healthy. In most cases there have been no calculi, and no constant predisposing factor has been observed.

Torsion occurs acutely and is associated with severe pain and shock. It leads to interference with the blood supply and is followed by gangrene and perforation of the gall-bladder.

TUMOURS OF THE GALL-BLADDER

Simple Tumours. Simple tumours of the gall-bladder are not uncommon, but from their small size and innocent nature they are often not recognized. Occasionally a benign *adenoma*, composed of columnar cells arranged in acini, is found near the fundus of the gall-bladder, forming a button-like prominence in the wall. A true *papilloma* is rare. *Lipoid papilloma* is the name sometimes given to the cholesterol-laden polypi of cholesterosis, but these are merely due to the aggregation of cholesterol in the villi, and are not to be regarded as tumours. True papillomata contain no lipoid material, but form small greenish projections on the mucous surface. Microscopically they have the character of papillary adenomata, with acini of columnar cells set in a well-formed stroma. Rarely such papillomata may be multiple, covering the whole surface of the gall-bladder, and in such cases they must be regarded as potentially malignant.

Malignant Tumours. Carcinoma is practically the only malignant tumour of the gall-bladder, although there are a few reported cases of sarcoma, melanoma and endothelioma, and one case which resembled a hypernephroma.

Carcinoma of the gall-bladder is now known to be far from rare. It is found in from 1% to 3.5% of surgical operations on the biliary tract, and comprises 2% to 5% of all cases of malignant disease seen at

autopsy. It is most common in women between the ages of fifty and sixty-five years.

The tumour is of special interest as one of the most striking examples of malignant disease developing as a sequel to chronic irritation, for it is almost invariably an end result of chronic cholecystitis, in most cases accompanied by gall-stones. There are many cases on record,



FIG. 250. Carcinoma of the gall-bladder invading the liver. The tumour, of scirrhus character, has caused a diffuse thickening of the gall-bladder and forms an ill-defined, pale mass infiltrating the liver. There is a large secondary growth in the cystic lymph gland. Note the association of gall-stones and carcinoma.

(Department of Surgery, University of Edinburgh.)

moreover, of carcinoma developing months or even years after operative removal of the stones.

Carcinoma of the gall-bladder spreads at an early stage beyond the confines of the gall-bladder, and soon oversteps the limits of successful removal. It invades the liver by direct continuity forming a large mass, sometimes 8 or 10 cm. in diameter, at its lower border. It spreads to the lymph glands along the cystic and common ducts, and thus may cause obstructive jaundice. In some cases it disseminates through the peritoneal cavity. Distant metastases are uncommon, except in the

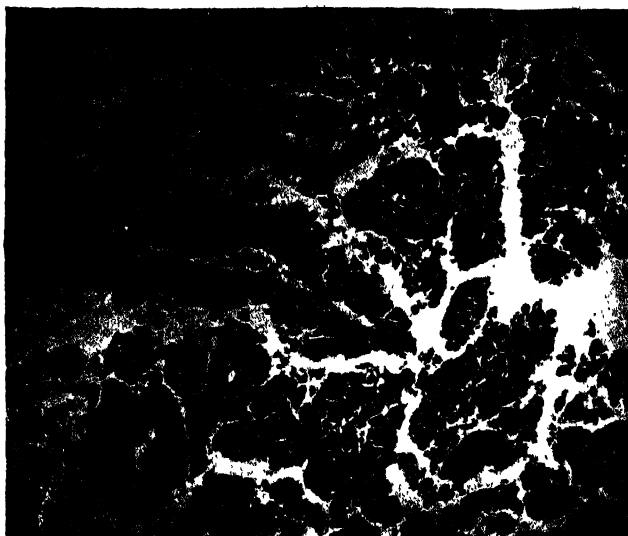


FIG. 251. Papillary adenocarcinoma of the gall-bladder. In places there are irregular glandular acini, whereas in other parts there is a definite papillary formation.

(Department of Surgery, University of Edinburgh.)

lungs, but there are a few cases on record of secondary growths in bones, and even in the breast.

Four types of carcinoma of the gall-bladder may be recognized.

(1) The *scirrhous carcinoma* is the commonest. It is a columnar-cell

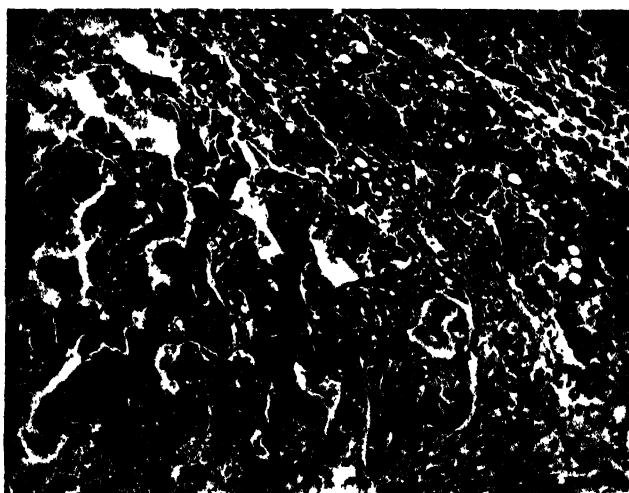


FIG. 252. Adenocarcinoma of the gall-bladder invading the liver. The columnar cells of the tumour (below) are arranged in irregular acini. The liver cells bordering on the tumour (top right) are flattened and atrophied, and those a little further away show various degrees of fatty degeneration.

(Department of Surgery, University of Edinburgh.)

adenocarcinoma with an acinar structure and a dense fibrous stroma, and it gives rise to a very hard growth which infiltrates the gall-bladder wall. At an early stage it forms a localized induration which may be mistaken for an area of chronic cholecystitis. In some cases it encircles and obstructs the cystic duct and may predispose to the development of empyema of the gall-bladder, or if it arises near the midpoint of the viscus it may give rise to an hour-glass deformity. Ultimately, in most cases, it completely envelops the gall-bladder and almost obliterates the lumen.

(2) *Papillary or proliferative carcinoma* is less common. It is an adenocarcinoma with a scanty stroma. The cells, columnar in shape, are arranged in irregular acini and may show a papillary arrangement. The growth is soft and often bulky, and tends to project into and fill the lumen of the gall-bladder.

(3) *Colloid carcinoma* is a soft tumour, recognizable by its gelatinous character. Sometimes the whole tumour is of colloid type, sometimes only a part is affected, and in some the condition is recognized only on microscopic examination. The cells, few in number, lie singly or in ill-formed acini, whilst the bulk of the tumour is made up of a structureless, blue-staining material, pseudomucin. The cells contain droplets of this substance in their cytoplasm, and some of them are distended to signet-ring shape.

(4) *Squamous carcinoma* (epithelioma) is a rare form of tumour, which presents characters similar to carcinoma of such squamous-cell membranes as the skin, the tongue or the œsophagus. The cells are of squamous type, there may be cell nests or epithelial pearls, and it is sometimes possible to identify typical prickly cells with intercellular bridges.

In some cases the whole tumour is of this type, in others only a part shows the squamous character, and there is a confusing appearance of areas of squamous epithelioma adjoining and merging into areas of columnar-cell adenocarcinoma.

Squamous epithelioma of the gall-bladder is generally regarded as an example of metaplasia, and it is thought possible that the growth arises in an area of the mucosa affected by leukoplakia as a result of the chronic irritation of gall-stones. Nicholson has pointed out that the development of squamous cells in a viscus of entodermal origin such as the gall-bladder has its analogy in the normal development of the œsophagus, which, like the rest of the foregut, is originally lined by columnar cells, but develops a squamous-cell membrane at an early stage of embryonic life.

ABSCESSSES IN THE LIVER

Solitary Abscess. Almost always this is a *tropical abscess* following amœbic dysentery, but in rare circumstances a single abscess may arise from other causes, as from the spread of infection from the gall-bladder, or from suppuration in a hydatid cyst, or from pyæmic infection.

A tropical abscess results from infection of the liver by amœbæ, which presumably reach this situation *viâ* the portal blood stream.

The disease affects Europeans living in the tropics with relatively greater frequency than the indigenous, and occasionally it has affected persons who have never visited the tropics. In 60% to 80% of cases the abscess develops in the right lobe of the liver, and often near its superior surface. It may attain large size, and is rarely recognized until several ounces of pus have collected. Rarely it may hold as much as 16 pints. The wall of the abscess is composed of necrotic liver tissue, and is usually shaggy and irregular. Later, much fibrous tissue develops and may form a fairly well-defined capsule. The pus may be of creamy appearance, but is usually chocolate-coloured from degenerating liver substance, and is often viscid and glairy. Amœbæ are present in the wall and adjacent liver tissue, but are often difficult to demonstrate.

Secondary perihepatitis usually develops, and the liver becomes fixed by adhesions to the diaphragm, abdominal wall and viscera. For this reason, downward displacement of the liver is unusual and the full extent of the enlargement is evidenced by radiographic demonstration of elevation of the diaphragm. The abscess may remain intact but often it ruptures, especially into the lung, pleura or peritoneum. Superadded infection with pyogenic organisms may occur.

Multiple Abscesses.

(1) *Pyæmic Abscesses*. These may occur in the course of any general pyæmia. They are scattered through all parts of the liver and are of small size, and as the liver affection is generally overshadowed by the severity of the general disease, they have little clinical significance.

(2) *Abscesses from Pylephlebitis and Portal Pyæmia*. Suppurative pylephlebitis results most often from appendicular infection, occasionally from suppurating lesions in the pelvis, *e.g.*, salpingitis, suppurating ovarian cysts, or even infected hæmorrhoids, and rarely from other intra-abdominal diseases. Males are affected most often, and most cases occur in the third decade. The disease follows infective thrombosis of the vessels near the original lesion, *e.g.*, the appendicular veins,

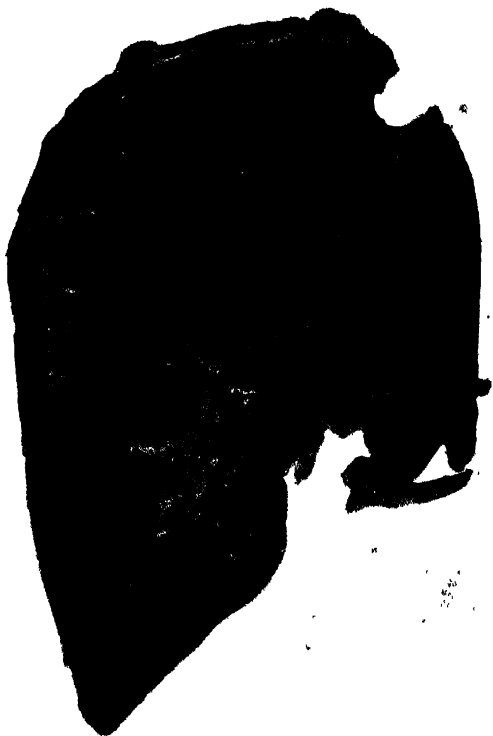


FIG. 253. Multiple abscesses in the liver, due to pylephlebitis.

(Museum of Royal College of Surgeons of Edinburgh.)

and from here it may extend to any part of the portal venous system, sometimes principally involving the extrahepatic vessels, sometimes the intrahepatic ones. The portal vein and its branches contain brownish pus mixed with breaking-down blood clot, their walls are swollen and acutely inflamed, and the perivascular tissues may also suppurate.

The liver is enlarged and tender. Its surface may be smooth, or nodular with numerous projecting abscesses, and it is usually adherent to the diaphragm and parietes. When cut it is seen to contain numerous abscesses, varying up to the size of walnuts, and between the cavities are pale yellow areas where the liver has undergone necrosis. Usually the abscesses are scattered through all parts of the liver, but sometimes one lobe, especially the right, may be more affected, a localization which probably depends in part upon the fact that the portal blood stream runs in currents, so that the blood from any one organ remains more or less separate and is diverted principally towards one or other lobe. Fortunately, the disease is very rare, for it almost invariably proves fatal, often from spread of the infection to the lung, pleura or peritoneum.

Portal pyæmia is the term used for a similar condition in which the abscesses are believed to be due to infected emboli in the portal stream rather than to direct infection along the vessel walls. It presents no distinctive features, however, and the two conditions are generally regarded as one.

(8) *Cholangitic Abscesses*. As the name indicates, these abscesses follow infection of the liver secondary to cholangitis, and consequently they are usually due to a gall-stone in the common duct. Rarely they result from other lesions associated with stagnation of the bile, such as the pressure of a tumour or, in the East, the presence of liver flukes or worms.

The liver is enlarged, and scattered through it are numerous greenish-yellow areas. Some of these are soft, but others are solid and may even resemble secondary malignant nodules. Sometimes the abscesses lie near the surface of the liver, and adjacent cavities may become confluent and reach larger size. The cavities communicate with bile ducts, into which they discharge their contents, and consequently the pus is deeply bile-coloured, and often mixed with "biliary mud."

Clinically, abscesses of this type are associated with the syndrome "Charcot's intermittent hepatic fever." Jaundice develops, of a peculiar ashy-grey type; the enlarged liver becomes tender and painful, the temperature swings intermittently, with frequent rigors; and there is severe toxæmia with sweating and rapid loss of weight.

CYSTS OF THE LIVER

There are two principal types of liver cyst, the parasitic and non-parasitic.

Parasitic cysts occur in hydatid disease, and the liver is the commonest site of this affection (see p. 50). Usually there is a single cyst, but occasionally multiple cysts are present. Hydatid cysts are most

common in the right lobe of the liver, and, according to Dew, they are situated towards its inferior aspect in 75% of cases. Consequently they tend to project towards the peritoneal cavity and become palpable through the abdominal wall. The cyst may be unilocular and contain no daughter cysts, but more often these are present, often in considerable numbers. Sometimes the cysts attain large size. They may rupture into the peritoneal cavity, into the biliary passages or the stomach, or through the diaphragm, but the commonest termination is calcification. Occasionally superadded septic infection of the cyst occurs.

Non-parasitic cysts are not uncommon, but being generally symptomless they rarely demand surgical attention. Three main types are recognized.

(1) *Cysts associated with polycystic disease of the kidneys* are nearly always multiple. The liver is greatly enlarged, and under its capsule project numerous cysts containing clear watery or blood-stained fluid. The cysts are of congenital origin, but may be of small size at birth and generally remain unrecognized until adult life, or even old age. They are said to be three times commoner in females than in males. Their mode of origin is not fully understood, but it seems probable that they are formed by the irregular proliferation of aberrant hypoblastic cells arising from the primitive biliary papilla.

(2) *Cysts associated with tumours* are seen in cystic adenoma of the liver, and occasionally in bile-duct carcinoma and other growths. There are one or two cases on record of teratomatous (dermoid) cyst.

(3) *Retention cysts* are generally solitary, or there may be a number of small cysts communicating with one large cavity. The cyst has a wall of fibrous tissue, often lined by a single layer of flattened epithelium, and it contains watery fluid, straw-coloured or sometimes blood-stained. The cyst does not communicate with the biliary system and therefore does not contain bile. Cysts of this type are generally regarded as due to retention within a small bile duct, the result of local obstruction by fibrosis. In most cases the cyst is small, and gives rise to no symptoms unless hæmorrhage occurs, when acute pain and fever may result. Occasionally a cyst reaches large size, and may contain as much as 13 pints of fluid. It may then exert pressure on neighbouring structures, the stomach, duodenum, portal vein, inferior vena cava, or even the right ureter.

GUMMA OF THE LIVER

The liver may be affected in inherited syphilis, or in the secondary or tertiary stages of acquired syphilis. From the surgical standpoint it is only necessary to consider the gummata of tertiary acquired disease.

Gummata are usually multiple, and arise principally near the surface of the liver under the capsule. They may be scattered in different parts of the liver, but usually the right lobe is particularly affected. In appearance and microscopic characters they do not differ from gummata elsewhere. They vary in size up to several centimetres in diameter, and are composed of dense fibrous tissue, often somewhat necrotic at the centre. Microscopically, it is seen that the smaller

gummata lie in the capsule of the liver and in its prolongations in the portal tracts. Surrounding the central necrotic portion is a well-developed zone of fibrous tissue, with areas of lymphocytic infiltration. Endarteritis obliterans is usually a striking feature in the adjacent blood vessels.

Gummata of the liver are of special importance surgically, owing to their tendency to mimic other biliary diseases. To the naked eye they are often indistinguishable from secondary malignant growths, and such confusion is all the more likely since the subjects of hepatic syphilis are often emaciated and cachectic. Gummata of the liver may simulate cholecystitis, for they may give rise to irregular fever and intermittent attacks of jaundice. Healing of a gumma is accompanied by extreme scarring, and this may cause obstructive jaundice and mimic the effects of a tumour of the common duct or of the pancreas.

ACTINOMYCOSIS OF THE LIVER

This is a rare affection, and is almost always secondary to actinomycotic disease of the intestinal tract. The lesions have the characteristics of actinomycosis elsewhere (*see* p. 46). The abscess is usually multilocular, and on section has the appearance of a honeycomb of yellow colour. The liver becomes adherent to the diaphragm or to the abdominal wall, and the abscess may rupture into the lung, into the stomach, or on the skin surface, especially after superadded infection.

PRIMARY TUMOURS OF THE LIVER

Simple Tumours. *Adenoma and angioma* are uncommon, and usually have little clinical importance. They may grow to large size, and may then cause symptoms from pressure. When situated near the inferior margin of the liver such a tumour may become pedunculated forming an obvious mobile intraperitoneal swelling of considerable size.

Primary Malignant Tumours.

Carcinoma may arise either from the liver cells or from the epithelium of the smaller bile ducts. Sarcoma also occurs. All varieties are rare, and every case requires critical observation to determine that it is not secondary to an obscure primary tumour. *Primary liver-cell cancer* is of interest, in that it is usually associated with cirrhosis or subacute atrophy of the liver. In these diseases a striking feature is the great regeneration of liver cells, and it appears that cancer arises when this process gets out of control, and when the proliferating liver cells throw off all restraining influences. The growth forms a large mass of soft solid tissue, very liable to undergo necrosis and softening. Usually the mass is single, but numerous secondary nodules develop in the rest of the liver. Metastases rarely appear in other organs. Microscopically, there are rounded masses of liver cells, which show irregular mitotic figures and other evidence of rapid growth.

Cancer arising in the intrahepatic bile ducts may closely resemble

liver-cell cancer. There is, however, usually no cirrhosis. The liver is enlarged and contains multiple nodules, each having the structure of a columnar-cell adenocarcinoma.

SECONDARY TUMOURS IN THE LIVER

The liver is more often affected by secondary tumours than any other viscus, and secondary tumours are very much more common than primary growths.

In the majority of cases the liver is involved by metastases derived from tumours within the portal area, and especially by carcinoma of the stomach, the colon, or the lower end of the œsophagus, in that order of relative frequency. Secondary growths from these three regions constitute about 50% of liver tumours. Less commonly the liver is involved by carcinoma of the gall-bladder, pancreas, lung, breast and kidney, and by sarcoma originating in other parts of the body.

As a rule secondary growths are multiple, and are scattered in all parts of the liver, but sometimes a solitary metastasis may attain considerable size before others appear. Occasionally one lobe of the liver is affected to a much greater extent than the remainder of the organ.

Small secondary nodules are usually of firm consistency, and are much harder than the surrounding liver tissue, through which they can readily be felt. As they increase in size the central parts, deprived of their blood supply, undergo degenerative changes and become softened, hence large metastases are often umbilicated. The growths are usually of pale colour, and sometimes pearly white, but occasionally, especially when of rapid growth, they are vascular and deep red. The natural features of such tumours as melanoma and chorionic carcinoma are usually reproduced in the metastases.

TUMOURS OF THE BILE DUCTS

The only bile-duct tumour in man is a *carcinoma*, which may arise from either the intrahepatic or the extrahepatic ducts. It is commoner in males than females and occurs usually in later life.

In the extrahepatic ducts the growth commonly arises either in the region of the duodenal ampulla or at the junction of the cystic with the common ducts. It forms a rounded hard swelling, rarely larger than a cherry, leading to a stricture and to complete obstruction of the duct. Death from obstructive jaundice usually occurs before the tumour metastasizes. Microscopically, it has the structure of a columnar-cell adenocarcinoma. If the growth is situated below the cystic duct, the gall-bladder, unless fibrous from previous cholecystitis, becomes distended, and if the growth lies above the level of the cystic duct the gall-bladder will be small or empty. At operation the great difficulty is to distinguish a small growth from a fibrous mass around a stone. If, as commonly happens, the growth is small and in the lower part of the duct, it may readily be overlooked.

Carcinoma of the intrahepatic bile ducts frequently takes the form of multiple small pale nodules, which appear to arise simultaneously.

It is distinguished with some difficulty from a primary liver-cell cancer, from which it differs in that it has columnar cells arranged round a definite lumen.

CYSTIC DILATATION OF THE COMMON BILE DUCT

This is a rare congenital abnormality which rarely comes to light until adolescence. It affects females four times more commonly than males. There is a dilatation like a saccular aneurysm, which is connected with the supraduodenal part of the common duct and forms a cystic swelling of variable size, sometimes as large as a man's head. As the cyst enlarges it stretches the duct system so that the hepatic ducts may open separately into the cyst above, and the common duct leaves it lower down. The cystic duct also may have a separate opening. The ducts above and below the cyst may be of normal calibre, but they are often dilated and tortuous, and the liver may be cirrhotic. The wall of the cyst in some cases is thin and translucent, transmitting the greenish colour of the bile; in others it is thick and fibrous, and may be studded with large calcified plaques and ulcers. The biliary content may be clear, or may be of the consistency of pea soup. There is usually no lining membrane, but there may be a layer of columnar cells, and even exceptionally squamous epithelium (Wilkie). As the cyst enlarges it follows the line of least resistance, and this is usually downwards and to the right, so that it raises the posterior parietal peritoneum of the right subhepatic fossa. The duodenum may be displaced downwards or may be stretched across the front of the cyst, and the right colic flexure displaced downwards and medially. Morley has described a case in which downward displacement of the small intestine stretched and constricted the root of the mesentery and gave rise to secondary duodenal ileus. The cyst may periodically become dilated, when it tends to kink and obstruct the common duct. Infection by coliform bacilli is a frequent complication and may prove fatal.

The diagnosis of a cyst of the common bile duct is suggested by the presence of a large cystic mass in the right hypochondrium, occurring in an adolescent girl and accompanied by recurring abdominal pain, intermittent jaundice, and sometimes fever.

JAUNDICE

Jaundice is the state characterized by an excess of bile pigment in the circulating blood and the tissues. Three types of jaundice are recognized:—

(1) *Hæmolytic*, exemplified in "acholuric jaundice" and other diseases of the spleen and reticulo-endothelial system. In these cases there is a simple excess of pigment, due to excessive destruction of the red blood cells. (2) *Toxi-infective*, for example, catarrhal jaundice and the jaundice due to metallic poisons. Here the main feature is degeneration of the polygonal cells of the liver. (3) *Obstructive*, as in occlusion of the bile ducts by stone or neoplasm. Here the bile, after being excreted, is reabsorbed from the ducts into the blood stream.

Obstructive Jaundice. From the surgical standpoint obstructive jaundice is the most important type, and its pathological features will be considered more fully. Obstructive jaundice may be caused by (1) foreign bodies within the common duct, such as stones or, rarely, parasites; (2) lesions of the common duct, such as carcinoma or, rarely, fibrous structure; (3) lesions compressing the common duct from without, such as carcinoma of the pancreas, secondary neoplasms, and, rarely, tuberculous or lymphadenomatous glands in the hilum of the liver.

Jaundice develops rapidly after the onset of obstruction to the biliary outflow, and may be evident by yellowness of the conjunctiva within a few hours. Then the skin becomes pigmented and the urine discoloured, and finally nearly every tissue is affected. The only unpigmented substances are certain secretions such as the saliva, the secretion of the common duct, and usually the milk and cerebrospinal fluid.

At first jaundice is slight, and the colour of the skin is light yellow, but in complete obstruction of long standing it deepens to an olive hue (black jaundice) owing to oxidization of the bilirubin to biliverdin. If cholangitis and intrahepatic suppuration follow, with toxæmia and cachexia, the colour turns to a sickly greenish-grey (grey jaundice).

Effects of Obstructive Jaundice. The effects of obstructive jaundice may be classified under four headings :—

- (1) Retention of the bile constituents.
- (2) Dilatation of the biliary system.
- (3) Impairment of liver function.
- (4) Alteration in blood coagulability.

(1) *Retention of the Bile Constituents.* All the bile constituents are retained, and may show an increase, temporary or permanent, in the blood. The bilirubin content of the blood rises from the normal of about 1 mg. to as much as 250 mg. per litre. Correspondingly, the icteric index may rise from the normal figure of 5 to over 200 units. If the jaundice continue during several weeks, the bilirubin content may finally show a slight decrease.

The bile salt content of the blood is also increased, and the cholesterol content of the blood may rise from the normal of about 150 mg. % to double that level. This is not, however, an invariable feature, and the blood cholesterol may remain within normal limits.

It is interesting to note that few of the pathological effects of jaundice can be ascribed to retention of the bile constituents. The bile salts are the only toxic constituents, but in most cases their increase in the blood is only transient. The bile pigments have been shown to be completely non-toxic even when present in large amount, whilst the cholesterol increase is no greater than may occur, for example, in pregnancy.

(2) *Dilatation of the Biliary System.* The first effect of obstruction is to raise the pressure within the whole biliary tract, and to distend the whole duct system, including all the fine biliary radicles within the liver (hydrohepatosis). This dilatation is usually most extreme when due to carcinoma, for infection is then often lacking and

the ducts are thin walled, whereas when stones are present there is usually infection and the ducts are thickened by fibrosis. The gall-bladder similarly is usually dilated when carcinoma is present, contracted by fibrous tissue when the obstruction is due to stones (Courvoisier's Law), but since carcinoma and stones may coexist this is by no means a dependable criterion.

If the obstruction is maintained a striking alteration occurs in the content of the duct system, and the bile becomes pale and colourless (white bile). When the pressure in the biliary tract reaches approximately 800 mm. of water, the liver is unable to continue its excretory function, and bile production ceases. The small glands in the walls of the common and hepatic ducts, which normally secrete a little clear fluid, are able to withstand a considerably higher pressure than this, and they continue to function, so that gradually the stagnant bile is replaced by their secretion. This is the so-called "white bile," a clear, watery, slightly alkaline fluid containing a trace of mucin, but no other bile constituent and no pigment. It is a striking feature, as Wilkie commented, that in a patient deeply jaundiced one of the few uncoloured substances in the body is this fluid in the common bile duct.

If the gall-bladder is absent or functionless through disease, this state of affairs is reached within a week from the onset of complete obstruction. On the other hand, a functioning gall-bladder delays the appearance of white bile for a much longer period. Sometimes when a healthy gall-bladder is present an intermediate stage is found. The gall-bladder contains green bile, but the content of the ducts is colourless.

(3) *Impairment of Liver Function.* Impairment of liver function constitutes one of the major dangers after operation upon cases of obstructive jaundice. The impairment is due partly to "back pressure" within the distended bile radicles, which leads to atrophy of the liver cells; partly, in some cases, to coincident infection. Thus we find evidence of liver dysfunction most marked in prolonged jaundice and when cholangitis is present—the latter a common occurrence in cases of stone in the common duct.

The liver function most obviously affected is glycogen storage, and the special risk of operation in obstructive jaundice arises from the fact that this is also the function most gravely affected by operative trauma and by certain anæsthetics. In some cases, the impairment of glycogen storage can be demonstrated by the lævulose tolerance test.

In the late stages of severe obstructive jaundice, all the manifold functions of the liver may suffer to some degree. The metabolism of fats and proteins is upset, poisonous nitrogenous products, which are normally converted by the liver into urea, remain in the circulation unchanged and cause secondary toxic effects upon the heart, kidneys and other organs, the alkali reserve of the blood is reduced, and eventually there supervenes a state of cholæmia, which closely resembles uræmia.

(4) *Alteration in Blood Coagulability.* It is well established that in obstructive jaundice there is a definite tendency towards hæmorrhages. This tendency is most noticeable in the late stages of deep jaundice due to malignant obstruction of the common duct, and it constitutes

one of the major risks of operation. Indeed, it has been stated that 50% of post-operative deaths in jaundice are due to this cause. The bleeding takes the form of an ooze from any incised or traumatized surface, and often leads to the formation of a hæmatoma in the depths of the wound.

It is remarkable that hæmorrhages are rare in cases not submitted to operation. It seems as though the trauma of the operation, or the added liver damage, or perhaps the sudden biliary decompression, in some way increases the risk of bleeding in the post-operative period.

The bleeding tendency in jaundice was formerly attributed to a deficiency of available calcium, which was believed to be "fixed" by the retained bile pigments. Recent work has shown, however, that the essential factor is a deficiency of prothrombin, and that this in turn results from a lack of an essential food factor, which has been termed the Koagulations-Vitamin or Vitamin K.

Deficiency of this food factor has been shown to be responsible for hæmorrhagic disorders in chickens and certain animals. In jaundice the deficiency arises partly from the fact that the vitamin, being fat-soluble, is not absorbed adequately in the absence of bile from the intestine; partly that, after absorption, it is not utilised in conditions of liver damage.

Chemical investigations have shown that the vitamin is a member of the naphthoquinone series. Other naphthoquinones, notably 2 : methyl-1·4-naphthoquinone, are equally active, and after intramuscular injection are effective in restoring the normal prothrombin level within a few hours.

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CHAPTER XXVIII

DISEASES OF THE PANCREAS

ACUTE PANCREATITIS (Acute Necrosis of the Pancreas)

ACUTE pancreatitis is one of the gravest of all acute abdominal diseases. It exceeds even perforation of a peptic ulcer in the sudden and dramatic illness it causes, the pain to which it gives rise is more agonizing, the patient's strength is depleted with greater rapidity, and shock and toxæmia are of earlier appearance and are more pronounced. In fulminating cases the mortality is about 50%, whilst in the less severe types the disability occasioned is severe and prolonged.

Acute pancreatitis is fortunately not very common. It affects males and females with about equal frequency and is most frequent between the ages of fifty and sixty years, though in exceptional cases it occurs much earlier.

Morbid Anatomy

The pathological changes in acute pancreatitis vary according to the intensity of the disease. Formerly it was the custom to describe three different types, hæmorrhagic, gangrenous and purulent, but this classification is somewhat misleading, in that gangrene or necrosis of the pancreas is an invariable feature, whilst hæmorrhage and suppuration are now regarded as secondary effects, varying in extent according to the intensity of the primary destructive change. In conformity with modern conceptions of the disease, therefore, it seems preferable to recognize two main varieties, the fulminating type, which is generally associated with hæmorrhages, and the subacute type, which may sometimes proceed to suppuration.

Fulminating Pancreatic Necrosis. In this type the disease originates with dramatic intensity and may bring about a fatal issue within two or three days. Operation or autopsy reveals extensive necrosis of the pancreas with hæmorrhages in the vicinity of the gland and a hæmorrhagic or turbid effusion into the peritoneal cavity, whilst spots of fat necrosis are seen in the extraperitoneal and omental tissues and in even more distant situations.

The *pancreas* is swollen and necrotic, soft and friable in consistency, purplish from extravasated blood or with a yellowish green tinge as a result of bile staining. In most fulminating cases the whole pancreas is involved, but occasionally the changes are limited to one portion of it. The connective tissues in the vicinity of the pancreas are tense with œdema or infiltrated with blood, whilst the adjacent peritoneal surfaces are deeply congested. Microscopically, the most conspicuous

change is necrosis of the parenchyma and interlobular septa, with hæmorrhages around the necrotic areas and in the surrounding areolar tissue. Evidence of an inflammatory reaction is notably lacking at this early stage and cultures usually prove sterile. Hyaline changes in the blood vessels are usual and there may be widespread thrombosis.

The hæmorrhages vary in extent, and in some cases are so great as to give the appearance of a diffuse retroperitoneal hæmatoma. Sometimes there are hæmorrhages also in other sites, for example in the abdominal wall, whilst occasionally the blood gravitates towards the loins and gives rise to discoloration of the skin in these regions.

The hæmorrhages are believed to occur as a result of degenerative changes brought about in the walls of blood vessels by enzymes liberated from the pancreas. Rich and Duff have drawn attention to a peculiar hyaline necrosis of the vessel walls, affecting particularly the muscle fibres of the media and the internal elastic lamina, and have shown that a similar lesion may be produced experimentally by the subcutaneous injection of trypsin.

Fat necrosis is one of the most characteristic changes in acute pancreatitis. It is most abundant in the neighbourhood of the pancreas but also occurs in the fat of the omentum, the transverse mesocolon and other extraperitoneal tissues or in the anterior abdominal wall. In these regions it has been attributed to the action of lipase liberated from the pancreas and permeating along lymph vessels. (Rarely, fat necrosis has been observed in more distant sites, such as the bone marrow, possibly as a result of excessive amounts of lipase carried in the bloodstream.)

In the vicinity of the pancreas the necrotic fat gives rise to greyish-yellow sloughs of cheesy or putty-like appearance. Elsewhere, the areas of necrosis take the form of small raised tallow-like spots, of firm consistency and yellowish-white colour. In these spots the neutral fats are saponified by lipase with the formation of glycerol and fatty acids; the latter form acicular crystals and may later combine with calcium to form insoluble soaps, which are deposited as globular masses and may reproduce the outline of the original cells. Eventually, if recovery occurs, these deposits may be reabsorbed.

The *biliary tract* often presents pathological changes in acute pancreatitis. Stones are found in the gall-bladder with a frequency variously estimated at from 40% to 70%, and it is remarkable that the stones are commonly of small size, the size of split peas or smaller. In occasional cases a stone is found in the common bile duct or impacted at the duodenal papilla. The gall-bladder may present slight chronic cholecystitis or be fibrous and contracted as a result of long-standing inflammation. The bile is usually dark in colour, muddy or blood-stained, and culture may reveal the presence of *B. coli*, streptococci, or sometimes *B. welchii*.

Subacute Pancreatic Necrosis. Here the pathological process is the same, but the disease proceeds less urgently, and recovery is usual. At operation, the pancreas is swollen and presents a brawny induration (if cut into, it is seen to be occupied by numerous small solid white foci of necrosis); the retroperitoneal tissues are oedematous, and there are

scattered spots of fat necrosis in the vicinity ; but these changes are less extensive than in the fulminating type and generally there are no hæmorrhages.

In some cases the disease affects the whole pancreas ; in others only a small portion is necrotic, and the secondary changes are correspondingly localized.

In cases seen two or three weeks after the onset of the disease, an abscess may be found, either in the retroperitoneal tissues or, more commonly, in the lesser peritoneal sac. Such an abscess contains thin pus or turbid watery fluid and there may be large grey sloughs, which probably consist of necrotic fat. The abscess is commonly sterile, and is thought to result from an aseptic inflammatory reaction caused by the presence of necrotic tissue, or by irritation of the peritoneum from escaped pancreatic ferments. It seems probable that the so-called false cyst of the pancreas (p. 586) often originates similarly, as a result of a mild or localized pancreatic necrosis.

Ætiology

The intensity of the pathological process, the lack of histological evidence of inflammatory change in the fulminating cases, and the negative bacteriological findings, all point to the conclusion that the disease is not primarily due to bacterial infection. It is now generally accepted that the condition is essentially an acute necrosis of the pancreas and is due to destruction of the glandular acini by the digestive action of its own juice. The pancreas secretes three enzymes, trypsin, diastase and lipase, and it is to the activity of the first-named that the auto-digestion is attributed. Normally, the trypsin is secreted in an inert form (trypsinogen), and is activated in the duodenum by the enzyme enterokinase. It is clear therefore that the cause of acute pancreatic necrosis is to be found in a study of the conditions under which the trypsin may be activated whilst still within the pancreas.

In 1901, Opie, of Johns Hopkins Hospital, reported a case of pancreatic necrosis in which he found a small gall-stone impacted at the duodenal papilla, and gave strong support to the view that the activation of pancreatic juice is caused by a reflux of bile into the pancreatic duct. This bile reflux theory has since been the subject of great controversy, and much interesting evidence has been collected both in favour of and against it.

It is well established that trypsinogen is activated by bile, especially if infected, and animal experimentation has shown that acute pancreatic necrosis can readily be produced by the injection of bile into the pancreatic duct. Trypsinogen can also be activated by many other agencies, including certain chemical substances and organisms such as *B. coli* ; but infected bile is far the most potent substance known and actually has a more powerful activating effect than enterokinase itself. It has been objected that experimental pancreatic necrosis can be produced only if the bile is injected under considerable pressure, which may well cause rupture of the pancreatic acini and escape of secretion into the interlobular connective tissues, but it may be observed that

bile is normally secreted at the pressure of 30 to 40 cm. H_2O and that the biliary pressure may be raised as high as 100 cm. by a forceful contraction of the gall-bladder. That mechanical rupture of the pancreatic acini is not the sole factor is shown by the observation that pancreatic necrosis cannot be produced by even forceful injection of bland substances.

Opie's suggestion that impaction of a gall-stone at the duodenal papilla might be a common aetiological factor has not been borne out by experience. Thus it is found that whereas gall-stones are commonly found in the gall-bladder (40% to 70%) and are commonly of such a size as to be capable of being carried down and impacting at the papilla, the demonstration of such an impacted stone is rarely possible (less than 5 per cent. of cases, according to Schmieden and Sebening), and even allowing for the likelihood that such a small concretion often escapes into the duodenum after determining the necrosis and thus fails to be observed, it is clear that only a minority of cases can be explained on such a basis. In this connection, however, it may be noted that pancreatic necrosis has been found associated with obstruction of the papilla by lesions other than stones, *e.g.*, a round worm.

Archibald suggested, as an explanation of cases in which no stone is found, that a similar obstruction, permitting reflux of bile along the pancreatic duct, might be produced by spasm of the sphincter of Oddi, such as might arise reflexly in the same way as pylorospasm in the course of cholecystitis. In support of this view he showed that in cats contraction of the sphincter of Oddi will withstand a pressure of 85 cm. H_2O , and that under these conditions infected bile introduced under pressure into the gall-bladder is forced up the pancreatic duct and regularly gives rise to pancreatic necrosis.

It is well known that the anatomical relationship of the bile and pancreatic ducts in man is not always of such a character as to permit bile reflux, and many observations have been made to determine the relative frequency of different types of ductal arrangement. The findings of different observers have been highly inconstant. Thus, Opie in 100 routine autopsy cases found an ampullary arrangement such as would allow the two duct systems to become confluent in 89, whereas Mann and Giordano placed the incidence at 8.5%—a low estimate which may perhaps be explained by the fact that they used formalin-hardened specimens without proper allowance for shrinkage of the ampullary tissues. Probably a more reliable estimate is that given by Cameron and Noble, who prepared casts of the ducts by injecting fusible metal after obstructing the papilla by means of a small stone; under these conditions the bile and pancreatic ducts were found to communicate in 75% of cases.

These anatomical variations in routine autopsies have, however, little bearing on the matter; far more important is the arrangement of the ducts in cases of pancreatic necrosis. Unfortunately, there have been very few observations on this subject, owing, no doubt, to the fact that in these cases the gland is friable and the ducts can be found with difficulty. Isolated cases have been reported, however, in which the

ducts opened separately into the duodenum, and rare cases have also been described of necrosis confined to the area drained by the accessory duct of Santorini. To explain such cases it has been suggested that the activation of trypsinogen might have been caused by reflux of intestinal contents from the duodenum, but it must be admitted that such an explanation lacks conviction.

Whilst the evidence cited above points clearly to a reflux of bile as the main ætiological factor in many cases of pancreatic necrosis, it cannot be regarded as a sufficient explanation in all. Apart from the direct evidence provided by the isolated examples already mentioned, in which the ducts have been shown to open separately into the duodenum, there are many cases in which the occurrence of biliary reflux would seem to have been improbable. Rich and Duff have drawn attention to a proliferative metaplasia of the duct epithelium similar to that seen in the breast in chronic mastitis, and have suggested that the obstruction of the pancreatic duct caused in this way may be responsible for the escape of trypsinogen into the intestinal tissues of the gland. On the other hand, the frequent association of pancreatic necrosis with chronic cholecystitis lends support to the old view, first put forward by Margaret, that a lymph-borne infection may sometimes be responsible for initiating the auto-digestion; whilst, finally, the occasional occurrence of pancreatic necrosis in the course of typhoid fever, mumps and other diseases suggests that in some cases a blood-borne infection may be an ætiological factor.

PANCREATIC CYSTS

Pancreatic cysts are rare. Their surgical importance lies in the fact that they must be taken into consideration in the differentiation of other cystic tumours in the abdomen.

It is customary to divide cysts of the pancreas into *true* and *false*, according as they arise in the gland itself or merely in proximity to it.

True Pancreatic Cysts

True pancreatic cysts are much rarer than false ones. They may originate in many different ways and the following varieties may be recognized: (1) Retention cysts. (2) Degeneration cysts. (3) Congenital cystic disease. (4) Dermoid cysts. (5) Hydatid cysts. (6) Hæmorrhagic cysts.

(1) **Retention Cysts.** Cystic dilatation of the ducts of the pancreas may result from obstruction by calculi, from fibrous stenosis of the main duct, and from chronic pancreatitis. The dilatation may be widely distributed but is rarely very great.

(2) **Degeneration Cysts** may arise either in an adenoma or in a carcinoma. The cyst is usually multilocular and is situated in the head of the pancreas. It contains clear or mucoid fluid, which may be blood-stained.

Multiple cysts are present very frequently in association with

angiomatous tumours of the cerebellum and spinal cord—Lindau's disease. Cysts or a hypernephroma may coexist in the kidneys.

(8) **Congenital cystic disease** is exceedingly rare; it has been found usually in children. The condition resembles that met with in the kidneys, with which it may coexist.

(4) and (5) **Dermoid and Hydatid cysts** have been found in the pancreas. They possess no special features other than those peculiar to the site in which they arise. A teratomatous cyst may occur in proximity to the pancreas.

(6) **Hæmorrhagic Cysts.** Bleeding may occur into the pancreas as a result of injury or from acute inflammation, and from either of these causes a cyst may develop; but blood may be found in almost any variety of pancreatic cyst.

False Pancreatic Cysts or Pseudocysts

A pseudocyst differs from a true cyst of the pancreas in that it does not originate in the substance of the gland but is situated in close proximity to it and is generally connected with it. At operation it may be difficult to determine the exact relationship of the cyst to the gland or, indeed, to be certain whether it is a true or false cyst. A true and a false cyst may be present in the same individual.

Ætiology. A pseudocyst is due usually to the encapsulation of extravasated fluid in the peripancreatic cellular tissues or in the omental bursa. Its mode of origin is not always clear as a satisfactory history cannot always be obtained. Many cases are due to injury, and follow a blow on the epigastrium which causes laceration of the posterior layer of the small peritoneal sac and of the pancreas. Blood and pancreatic secretions are poured into the omental bursa or into the cellular tissues around the pancreas; the epiploic foramen becomes sealed, and the peritoneum becomes condensed around the effusion and brings about its encapsulation. The resulting swelling in the upper part of the abdominal cavity may be evident within a few days or a few weeks of injury, or it may not be detected for many months. In some cases the origin of a pancreatic cyst may be traced to a mild attack of pancreatitis, which causes an outpouring of blood and pancreatic ferments into the tissues around the pancreas.

Pathological Features. A false pancreatic cyst varies in size from an orange to larger than a foetal head. The thickness of the cyst wall varies, but usually it is quite thin; its lining is generally smooth, although ridges and septa are sometimes present. Old blood clot may adhere in places to the wall of the cyst. Some cysts are multilocular. The lining of the cyst is sometimes composed of cylindrical epithelium, but in many it is fibrous. The contents of the cyst may be clear and watery or gelatinous but more often are light brown from extravasated blood. In a few instances the fluid may have a green tinge from the presence of bile. The fluid contains albumen, is alkaline in reaction and of low specific gravity, and on analysis is found to contain very little solid matter. The most important character of the fluid is its faculty of digestion. All three pancreatic ferments may be present,

but often there is only one. In some, especially old encapsuled cysts, no ferments are found, or the ferments may be present in an inactivated form. The presence of all three ferments points to a cyst arising from or directly connected with the pancreas, but their absence does not exclude a pancreatic origin. The finding of a starch-converting ferment alone is of little value in diagnosis, because it has been shown that fluid from other abdominal cysts or even ascitic fluid may possess such properties. (It is a familiar observation that when a pancreatic cyst is drained excoriation of the skin and digestion of the subcutaneous tissues may occur from the leakage of the enzyme-containing fluid,

A pancreatic cyst may arise in or be related to any part of the gland, but most frequently it is in the neighbourhood of the body or the tail. In the majority the cyst lies behind the posterior layer of the peritoneum forming the omental bursa. The ultimate position and relations of the cyst are determined by its relations to the peritoneal reflections which form the omental bursa. Thus a cyst may protrude between the stomach and liver; or (and this is most frequent) between the stomach and transverse colon. Occasionally it has entered the layers of the transverse mesocolon, and the colon is stretched over its surface. A cyst in the head may cause pressure on the common bile duct and jaundice. The many variations in position lead to great difficulty in differential diagnosis, and to confusion with other abdominal cysts—for example, a dilated gall-bladder, a cyst of the common bile duct, a cyst of the posterior wall of the stomach, a collection of ascitic fluid and hydronephrosis. Spontaneous rupture is a rare occurrence.

In the treatment of a pancreatic cyst, marsupialization of the cyst wall and drainage are usually sufficient. Complete removal of a large cyst, unless it is pedunculated, may be attended by great risk on account of the large and often dilated vessels that surround it and because of its firm adhesion to neighbouring structures.

PANCREATIC CALCULI

Calculi in the pancreatic ducts are rare. Men are affected more often than women (4 : 1).

Calculi are never found in a healthy pancreas, and it seems probable that they are the result of catarrh of the ducts from infection. The number of calculi varies, usually five to ten are present; in rare cases there is a solitary calculus, but as many as 800 have been found. The calculi vary in size from fine gritty material to masses the size of a date stone or a walnut. They may be smooth or rough, soft or hard, and in colour white, grey or yellow.

A pancreatic calculus is chiefly composed of phosphate and carbonate of calcium, but examples containing oxalates are described. On account of their content of lime salts they cast a shadow in a radiogram, and this is helpful in their recognition.

The calculi may be found in all parts of the ducts of the pancreas, but the head is the usual site.

A pancreatic calculus may give rise to symptoms which closely

resemble biliary colic. In many of the recorded cases gall-stones have been present, sometimes with jaundice, and this has diverted attention from the pancreas. In some the presence of glycosuria, azotorrhœa and steatorrhœa may aid in diagnosis by directing particular attention to the pancreas. Sometimes a calculus has been responsible for an abscess.

In diagnosis the presence of a shadow in the region of the pancreas may be helpful. A single calculus in the head usually lies transversely. If the calculi are more numerous and distributed throughout the pancreas diagnosis may be made with considerable certainty.

TUMOURS OF THE PANCREAS

Simple Tumours

Simple tumours of the pancreas are rare, but as they are usually encapsuled they are amenable to surgical removal. The commonest is an adenoma, which is often cystic (*cystadenoma*). It originates probably in the duct epithelium, and has been found most often in relation to the head of the gland.

Islet-cell Tumour (*Nesidioblastoma*). A simple adenoma may arise in the islet tissue of the pancreas. It may possess exaggerated functional activity and give rise to characteristic metabolic and clinical features which are known as *hyperinsulinism*. The disease is commonest in middle-aged adults, especially women.

The adenoma is usually greyish-white or pink and ovoid, and may be 2-9 cm. in its long axis. It is most common in the body or tail on the superficial surface, but it may be deeply seated in any part of the gland. The tumour has usually a thin capsule, but in some instances local infiltration has been observed; but definite malignancy with metastasis is very rare. Microscopically, an islet-cell adenoma is composed chiefly of branching solid trabeculae two or more cells thick, and separated by strands of fibrous tissue rich in blood vessels. The cells are mostly basophilic and resemble the normal β cells of the islets, and are polyhedral or columnar with abundant granular cytoplasm containing a round or oval nucleus which stains deeply with hæmatoxylin.

An islet-cell tumour may give rise to periodic attacks like those due to an overdose of insulin and characterized by dizziness, somnolence, etc. The attacks may be precipitated by prolonged fasting, and when they occur they may be relieved by giving large quantities of glucose. The blood-sugar is constantly low, varying between 0.02% and 0.05%.

In cases of suspected hyperinsulinism, provided other causes of hypoglycæmia can be excluded, surgical exploration is warranted; and in the cases in which the tumour has been removed and the patient survived there has been complete recovery. At operation discovery of the tumour may be difficult, or, if it is deeply embedded, impossible. There may be more than one tumour. In some cases there is no tumour but generalized overgrowth of the islet-tissue.

Malignant Tumours

The pancreas, especially its head, is very frequently involved by the extension of a carcinoma of the stomach, and such a growth is more common than a primary malignant tumour. Metastatic tumours from the lung, breast, etc., are common.

Types of Growth. A primary carcinoma may begin in the glandular epithelium or in the cells lining the excretory ducts, and the microscopic structure is determined by this difference in origin. A cancer arising from the glandular epithelium is of a spheroidal-cell pattern; it is

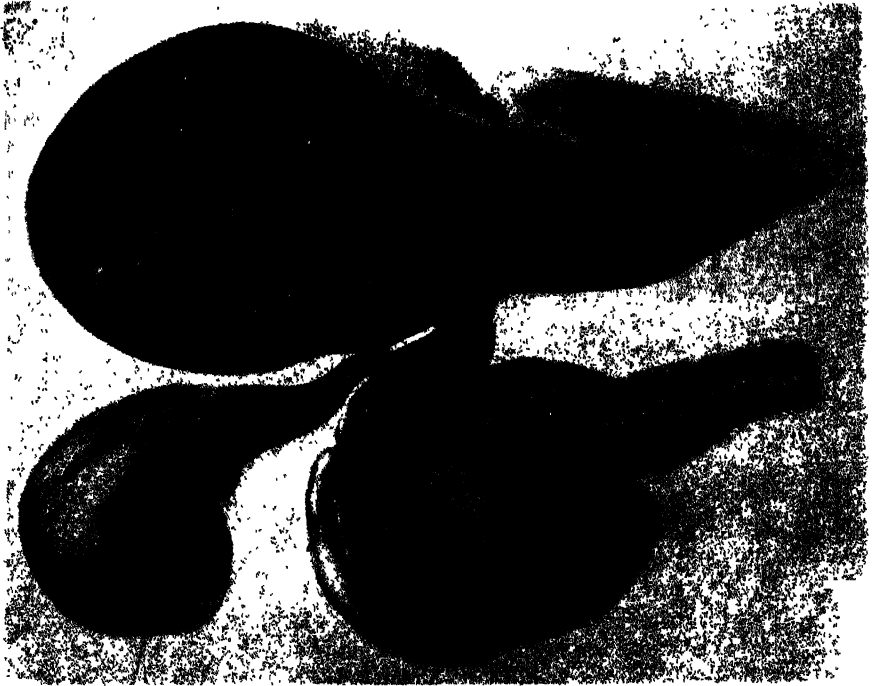


FIG. 254. Carcinoma in the head of the pancreas. The tumour is small and has occluded both the pancreatic and the common bile duct. There is a very marked dilatation of the common bile duct and the intrahepatic ducts: the gall-bladder is moderately dilated.

much more common and is of more rapid growth than the columnar-cell type derived from the ducts. The spheroidal-cell tumours are usually of a scirrhus type, although a bulky encephaloid tumour is sometimes observed. In all varieties mucoid, cystic or hæmorrhagic changes may occur. Calculi have been discovered in the interior of some tumours, and have been held responsible for their development.

Malignant tumours seldom attain a very large size. The growth is usually hard, irregular, and nodular on its surface, and it is securely fixed to neighbouring structures. The cut surface of the tumour is usually of whitish-grey or yellow colour, and degenerative changes are

often noted in it. In about 56% of cases the tumour is in the head of the pancreas, the body is the next most common site (6%), and the tail is but rarely involved. In a considerable proportion (80%) the whole gland is involved diffusely by a multi-nodular type of growth that causes a generalized and fairly uniform enlargement of the pancreas.

Pathological Effects. The pathological effects vary according to the situation and the direction of extension of the tumour. When, as is most common, the growth is in the head it causes compression of the pancreatic duct and may obliterate it completely so that at autopsy the whole duct system proximally may be widely dilated. The common bile duct is usually subjected to pressure or compression at an early stage, although its involvement may be long delayed or may never occur. Obstruction of the common bile duct leads to a dilatation of the upper part of the duct and gradually increasing distension of the gall-bladder, and in the later stages the intrahepatic ducts are considerably dilated. It is unusual for the tumour to cause much obstruction of the duodenum. Emptying of the stomach may be interfered with from involvement of the pylorus.

A tumour in the head of the pancreas as it extends may occlude the portal vein of its tributaries, or even the vena cava, and ascites is often found as a late feature. Portal thrombosis has occurred in a few instances. The ureter, colon or stomach may be invaded in the late stages.

Secondary deposits occur with greatest frequency in the liver, either as multiple opaque foci or, more rarely, as a single large mass. The retroperitoneal lymph glands are often involved and through that channel the mediastinal glands may be invaded. In advanced cases metastases of considerable size may occur in the lungs.

Clinico-pathological Features. The signs and symptoms are governed by the position of the tumour. When it attains considerable size it may be palpated from the front, but the common scirrhus type of growth in the head of the pancreas is often very small and may be difficult to detect at operation. The gradual onset of jaundice with obvious enlargement of the liver and the gall-bladder is the most striking effect. No matter where the tumour is situated, emaciation is very rapid and is out of proportion to its size and rate of growth.

A tumour in the body of the gland usually causes pain and a gradual failure of appetite and strength, features which make differentiation from carcinoma of the stomach difficult.

From the surgical standpoint malignant tumours of the pancreas, on account of the secluded position and infiltrative characters, are seldom amenable to other than palliative measures. There are occasional exceptions when the tumour is situated in the body or tail of the gland. Recently it has been proved that permanent ligation of the pancreatic duct with resulting atrophy of glandular tissue may not disturb digestion. Such assurances may stimulate greater boldness in dealing with tumours in the head of the pancreas.

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CHAPTER XXIX

DISEASES OF THE SPLEEN

THE surgery of the spleen, formerly based upon pure empiricism, has now passed the experimental stage and is founded on scientific pathological and hæmatological precepts.

Structure. The structure of the spleen appears very confusing to those unacquainted with its architecture, but actually it is not unduly complicated. The thick fibro-muscular capsule and trabeculæ enclose a network of branching cells which form the framework of the pulp, and scattered through the pulp lie the Malpighian bodies, which consist of localized thickenings of lymphoid tissue arranged like mantles around the smaller arteries. The structure may best be understood by considering the course of the blood stream. The arteries, after giving off small side branches which terminate in the Malpighian bodies, branch in a dichotomous manner, and end in minute penicillar vessels little larger than capillaries, which are surrounded by aggregations of pulp cells known as ellipsoids. From there the blood passes into a meshwork of wide tortuous channels, the sinusoids of the pulp, which have no complete endothelial lining and are essentially clefts between the branching reticulate pulp cells. The sinusoids are of large size compared with the penicillar vessels, and the blood therefore pursues a sluggish course, in places even stagnating for relatively long periods; the blood is thus brought into intimate contact with the pulp cells, and is readily subjected to their beneficent influences. Finally, the blood leaving the pulp spaces is collected into large venous sinuses and thence to the tributaries of the splenic vein.

Functions. The spleen is not a separate and independent viscus, working in isolation and having specific properties, but rather as an organ intimately connected with at least three important systems. It is the most important member of the reticulo-endothelial system, it takes part in the formation of the blood, especially in the embryo, and it is intimately concerned with the metabolism of blood pigment. Consequently, it shares in a special degree the same changes as other organs concerned with hæmatopœsis.

The functions of the spleen, so far as they are known or suspected, may be classified as follows:—

(1) *Hæmatopoietic Function.* In adult life this is practically confined to the production of lymphocytes in the Malpighian bodies. (Occasionally in disease the spleen may resume its embryonic property of producing red cells and polymorph leucocytes.)

(2) *Hæmatoclastic Function.* As the most important member of the reticulo-endothelial system the spleen is the principal organ concerned with the destruction of blood corpuscles. Effete red cells are held up

in the meshes of the pulp and are here subjected to destructive influences. Their hæmoglobin content is set free, and becomes converted into intermediate products, which are either stored or despatched to the liver for excretion in the bile. Probably the spleen also destroys blood platelets, for it is found that in diseases characterized by a great diminution in platelets removal of the spleen is followed by their reappearance in normal numbers.

(8) *Phagocytosis of Particulate Matter.* In its sluggish flow through the sinusoids, the blood comes into intimate contact with the phagocytic cells of the pulp, and these exercise the most important action of removing organisms and other foreign or noxious particles present in the circulating fluids. This phagocytic action may be demonstrated readily in the animal by injecting some particulate substance such as Indian ink into the blood stream, when the spleen rapidly becomes loaded with pigment and assumes a deep black hue. This may be of importance as a protective mechanism in infective diseases and in the continual minor disturbances of everyday life.

(4) *Reservoir Function.* The capsule and trabeculae contain plain muscle fibres embedded in the connective tissue, and in virtue of these the spleen is an actively contractile organ which, in response to certain stimuli, undergoes reduction in size to a very considerable extent. The importance of this property lies in the fact that in health when the body is at rest the spleen contains a large fraction of the total blood volume—occasionally, it is claimed, as much as one-fifth—and when under certain conditions the need for this blood arises the spleen is able to expel it into the portal circulation.

These variations in size serve to regulate the degree of congestion of the liver and the alimentary canal during the phases of digestion, and also enable the spleen to respond to the demand for sudden increase in the red cell content of the circulating blood, for example, during exercise and in asphyxia, carbon monoxide poisoning and hæmorrhage.

(5) *Effect on Fragility of Red Cells.* Red cells expressed from the splenic pulp are more fragile than those circulating in the blood stream, as estimated by their readier lysis when placed in graduated hypotonic salt solutions. Moreover, in conditions characterized by excessive fragility of the circulating red blood cells it is found that removal of the spleen is generally followed by a return of the cells almost, or entirely, to their normal state. These observations have suggested that the spleen normally, and in certain diseases to a greater degree, increases the fragility of the red cells.

(6) *Production of Antibodies.* In certain animals it is found that splenectomy is followed by a diminished resistance to infections, and it has been thought that the spleen may be an important site for the production of antibodies. Confirmation, however, is lacking.

Effects of Splenectomy. Removal of the spleen is followed by temporary leucocytosis and temporary anæmia of the secondary type. These disturbances usually pass off in a few weeks but occasionally persist during several months. When the blood platelets have been reduced in number before operation there is a rapid return to the normal (200,000 per c. mm.), but when the number before operation

has been normal there is usually little change, though sometimes an increase even to fivefold has been noted, and this probably predisposes to thrombosis. The fragility of the red cells is decreased in the healthy animal after splenectomy, and the same sometimes is observed in man, particularly if increased fragility has been present before operation.

One of the most valuable effects of splenectomy is a purely mechanical one, namely, that of eliminating the splenic blood flow and thus diminishing the quantity of blood reaching the liver. It is said that in health the spleen transmits a quarter of the portal blood, and when the spleen is large and very vascular, as in splenic anæmia, the proportion transmitted must be much greater. To a liver embarrassed by cirrhotic change the reduction of the portal circulation must bring great relief.

The Rationale of Splenectomy. Except in injuries or in undue mobility of the spleen, splenectomy should only be advised upon some definite indication based upon pathological considerations. The days of splenectomy for mere splenomegaly are past, and in practice there are three major indications for the operation :—

- (1) To remove a focus of disease, *e.g.*, a tumour or cyst.
- (2) To reduce the volume of blood in the portal circulation.
- (3) When there is evidence that the spleen is engaged in excessive destruction of, or damage to, the cells of the blood.

The last indication is of especial importance in atypical disorders of the spleen and blood-forming tissues. In progressive anæmia of unknown origin with a large spleen it is essential to decide whether the spleen is primarily involved and is the cause of the anæmia, or whether the splenic enlargement is compensatory. In such a case much can be learnt from two diagnostic procedures, namely, estimation of the fragility of the blood cells and enumeration of the reticulocytes.

The fragility of the red cells is measured by their resistance to hypotonic saline solutions. Normal blood added to a graduated series of saline solutions lyses when the concentration of sodium chloride is reduced to about 0.35% or 0.4%, but fragile cells lyse more readily, at 0.5% or 0.6%.

The reticulocyte count is even more valuable. A reticulocyte is merely an immature red cell, and it differs from the adult cell in possessing a delicate reticulum, which is invisible in films stained by the usual methods, but can be demonstrated readily by the use of vital stains. It is probable that all red cells are at first reticulate, but in health reticulocytes are present in only very small numbers in the circulating blood. An increased count indicates an exaggerated erythroblastic activity of the bone marrow.

In aplastic anæmia or where the bone marrow is diseased and unable to proliferate, no reticulocytes are formed, whereas in acholuric jaundice, when the bone marrow is attempting to replace the cells destroyed in the spleen, the count may rise even to 85%. In progressive anæmia a high reticulocyte count indicates that if the hæmolytic agent be removed, the bone marrow will adequately recover its normal activity.

INJURIES OF THE SPLEEN

The spleen may be pierced in stab wounds, or rarely by a sharp fragment of a broken rib forced inwards through the diaphragm. A much more common injury, however, is rupture of the spleen resulting from indirect violence. Rupture of the spleen generally occurs as a result of a severe crushing or "run over" injury, and it may be accompanied by other injuries, such as fractured ribs, rupture of the liver, a tear of the diaphragm or a fracture of the spine. An enlarged spleen, especially one which is soft and friable from disease, may be ruptured by a comparatively slight injury, or even spontaneously—perhaps as a result of a sudden contraction of the plain muscle fibres in its capsule. Rare cases have been described of spontaneous rupture of a normal spleen.

The rupture generally involves the vascular pedicle of the spleen and leads to hæmorrhage into the peritoneal cavity. At first the bleeding is slow, owing to the degree of shock caused by the injury, and a hæmatoma forms in the left upper quadrant of the abdomen; but after a few hours, when the blood pressure rises, the bleeding becomes more profuse. In rare cases the severe hæmorrhage may be delayed a day or two, or even a week.

EXCESSIVE MOBILITY OF THE SPLEEN

A spleen enlarged from any cause, and occasionally a spleen of normal size, may stretch its retaining ligaments and attain considerable mobility, so that it swings freely to any part of the peritoneal cavity. Such a spleen may cause discomfort on account of its weight and mobility, and, moreover, it is apt to give rise to symptoms from torsion of its pedicle. Such a mobile spleen may rarely give rise to secondary effects from pressure. Cases have even been recorded in which the spleen became impacted in the pelvis, and pressed upon the bladder and rectum.

CYSTS OF THE SPLEEN

Cysts of the spleen are rare, and their origin is obscure. The majority are spurious cysts, the result of hæmorrhage into the substance of the spleen or of degenerative changes from infectious or vascular disease. Hydatid cysts and dermoid cysts have been described from time to time.

Primary non-parasitic cysts may be classified as single or multiple. Single cysts, which are rare, have been observed generally in young adults. They may attain considerable size and may fill the greater part of the abdomen, so as to be mistaken for an ovarian cyst. Such cysts contain serous fluid often loaded with cholesterol crystals. The cyst may have an endothelial, epidermoid or a fibrous lining, or a combination of all.

Multiple cysts of the spleen sometimes occur in association with polycystic disease of the kidneys and liver.

TUMOURS OF THE SPLEEN

Primary tumours in the spleen are extremely rare. Carcinoma, sarcoma, and angioma have been described. Of secondary tumours, those arising in hæmatopoietic tissues, *e.g.*, multiple myeloma, are the most common. Occasionally the spleen is involved in tumours growing from neighbouring organs, such as the stomach or the left kidney.

The rarity of tumours of the spleen presents a problem of great interest in relation to the general features of cancer growth, for although the spleen has lymph vessels only about its capsule, its blood supply is copious, and one would expect it to afford a favourable site for proliferation of cancer emboli. There is no doubt that many cancer cells reach the spleen, but fail to establish themselves, and it would seem that the spleen possesses a not yet understood property of inhibiting their growth. In this respect it resembles muscle which too is another rare site of secondary tumours.

OTHER SURGICAL DISEASES OF THE SPLEEN

There remain for consideration certain affections of doubtful nature, which are characterized by a variable degree of enlargement of the spleen and by many more widespread changes. Certain of these may be regarded as primary diseases, others are diseases in which the spleen merely participates. The classification of these diseases presents many difficulties owing to the diversity of their manifestations, which, moreover, differ in detail in almost every individual case; and their ætiology constitutes one of the most difficult problems of hæmatology. For simplicity, however, it will suffice here to describe only those of surgical interest, *viz.*: (1) acholuric jaundice with erythrocytic fragility; (2) splenic anæmia; (3) thrombocytopenic purpura.

A fourth condition, the distinct entity known as Egyptian splenomegaly, is outside the scope of this book, and it will be sufficient to state that it is believed to result from schistosomiasis (bilharziasis), and that in its pathology and clinical effects it closely resembles splenic anæmia.

ACHOLURIC OR HÆMOLYTIC JAUNDICE WITH FRAGILITY OF RED CELLS

There are many types of hæmolytic jaundice, but the only one of surgical interest is that associated with fragility of the erythrocytes. This is usually congenital, and then often familial, but it may be an acquired affection. It is characterized by mild jaundice, variable in degree but persistent throughout life, secondary anæmia and moderate enlargement of the spleen.

The essential feature of the disease is an increase in the fragility of the red blood cells. When blood is added to hypotonic salt solutions of gradually diminishing strength, a stage is reached at which lysis or laking of the red cells begins. In health, this point is reached when the concentration of sodium chloride is reduced to 0.35% or 0.4%, whereas in conditions of undue fragility it is reached earlier at perhaps 0.5% or 0.6%.

The effect of this fragility is to cause an excessive breaking down of the abnormal cells by the spleen, with consequent liberation of excessive amounts of blood pigment. There is an excess of a pigment closely related to bilirubin in the blood, and the bile is heavily laden with pigment. The fæces remain coloured, and, as the bilirubinæmia is of mild degree, there is no overflow of bile pigments into the urine. To compensate for this hæmolysis the bone marrow rapidly discharges young red cells into the circulation, and consequently the reticulocyte count may be increased, even to 85% (see p. 594).

Where the disease is congenital, the symptoms are usually mild, and slight jaundice with anæmia is the only manifestation. In some cases, however, and more commonly in the acquired form of the disease the anæmia is more severe, and there may be occasional exacerbations of the jaundice with pain in the upper abdomen and fever, which may simulate cholelithiasis. In many cases gall-stones are formed as the result of the disturbance of pigment metabolism. The stones are of the "pure pigment" type (see p. 562).

The spleen is invariably enlarged in acholuric jaundice, usually only to a moderate degree, occasionally to ten times its former bulk. Adhesions are rarely present. Microscopically, the only gross change usually found is a marked increase in the vascularity of the pulp, but if the spleen has been removed during an active phase of the disease there may be an excess of blood pigment.

The disease is now regarded as due to the formation in the bone-marrow of defective and unduly fragile red cells which readily undergo lysis, and it is believed that the spleen enlarges in an attempt to remove these excessively fragile cells from the circulation. The acquired disease, however, may be due to a primary increase in the functional activity of the spleen, an increased avidity for red cells and a true "hypersplenism" (Parkes Weber).

Whatever the cause, splenectomy is the rational line of treatment in the great majority of cases. The jaundice rapidly fades, and in a few months the blood count returns to normal. Usually the fragility of the cells shows a slow return almost, if not completely, to the normal. Occasionally, however, although all other manifestations of the disease disappear, the excessive fragility remains.

SPLENIC ANÆMIA (Banti's Disease)

Splenic anæmia is not now regarded as a distinct entity, but rather as an indefinite group of diseases, for there is considerable variation in both the clinical and pathological features. For the sake of clearness, however, a fairly typical picture may be sketched as follows: The disease is characterized by enlargement of the spleen and secondary anæmia, followed later by cirrhosis of the liver and ascites. Clinically, three stages are described. In the first stage there is gradual enlargement of the spleen, accompanied or followed by anæmia of secondary type, but by no other disturbance of general health. After a variable period, which may be many years, the second stage sets in, which occurs at the time when the disease is beginning to affect the liver. The liver becomes enlarged from early cirrhotic changes, and the general health shows

signs of impairment. In the third stage the liver becomes more obviously involved by cirrhosis and diminishes in size. Ascites and jaundice appear as late complications.

The spleen is considerably enlarged, and may reach to the umbilicus, it is grey-pink in colour and of firm consistency. Microscopically, there are areas of fibrosis, particularly around the central arterioles of the Malpighian corpuscles. The fibrotic areas contain particles of iron pigment—amorphous deposits of carbonate and oxides of iron, and crystals of ferric phosphate—and on this account are known as siderotic nodules. They are believed to be caused by peri-arterial hæmorrhages, due to venous congestion.

Surgically, the condition of the vascular pedicle is of the utmost importance. The veins are especially affected, and both the tributaries of the splenic vein, and the short gastric vessels running from the hilum of the spleen towards the greater curvature of the stomach, are greatly dilated and tortuous. One large vein at the upper end of the gastrosplenic ligament often seems to be particularly prominent, and since enlargement of the spleen has the effect of shortening this ligament so that the greater curvature of the stomach and the spleen almost touch, ligation of this vessel may prove troublesome. The walls of the veins are usually the seat of thrombophlebitis, rendering them brittle and easily torn, and the portal vein may share in this affection. Adhesions between the spleen and the diaphragm are said to be common, but their frequency has probably been over-estimated.

The blood changes in splenic anæmia are not characteristic. There is secondary anæmia, often to the extent of 3,000,000 red cells per c. mm., and there is nearly always some degree of leucopenia. An important feature of the disease is a tendency to hæmorrhage. Hæmatemesis, which is especially common, is usually related to the presence of dilated veins on the greater curvature or in the œsophagus, but bleeding may occur from other situations, when it is presumably due to changes in the bleeding time. Rosenthal claims that two types of blood change occur. In the one (thrombocytopenic type) there is diminution or even absence of blood platelets, and a consequent liability to hæmorrhages; in the other (thrombocythæmic type) the platelet count is normal or slightly raised, and there is no tendency to bleed. The recognition of these two types is significant in another respect, in relation to the not uncommon post-operative complication of excessive thrombosis. In the thrombocythæmic variety the platelet count may rise after operation to very high figures, from the normal of about 200,000 to as much as a million per c. mm., and the tendency to thrombosis may therefore be considerable. In the thrombocytopenic variety, on the other hand, the post-operative increase of platelets does not greatly surpass the normal level, and thrombosis is consequently less apt to occur.

As has been indicated above, the term "splenic anæmia" represents a hæmatological rubbish heap. "Hepato-lienal fibrosis" is a better title. Pathological changes in the spleen are identical with those found in the enlarged spleen of hobnail cirrhosis of the liver, and there is much evidence to suggest that the two diseases are closely related.

Banti regarded the splenic enlargement as inflammatory in origin, but the modern view is that the splenic changes are secondary to a hepatitis which only manifests itself in obvious cirrhosis after a long period. It has been suggested that hepatitis affects the spleen in two distinct ways, first by venous back pressure in the portal system, and secondly by pouring out toxins into the blood stream, which affect the spleen as a member of the reticulo-endothelial system.

THROMBOCYTOPENIC PURPURA (Essential Thrombopenia)

There are many forms of purpura, that is, of diseases characterized by a tendency to hæmorrhagic extravasations. In some, the changes in the blood are obviously secondary, as in the case of the so-called symptomatic purpura of septicæmia, miliary tuberculosis, etc.; in others, the blood changes appear to be primary.

The only variety of surgical interest is one of the primary group which is known as thrombocytopenic purpura. This is a disease manifesting itself intermittently in otherwise healthy persons, usually adolescents, and clinically characterized by cutaneous hæmorrhages, slight recurring fever, and splenomegaly. The blood changes during the attacks are characteristic. The essential feature is a decrease in the number of platelets (thrombocytes) almost to zero, and this results in marked increase in the bleeding time as estimated by the duration of flow of blood from a small puncture of the lobule of the ear. From the normal range of 2 to 4 minutes this may be increased to 15 minutes or longer. It is a remarkable fact that although bleeding from the capillaries is so prolonged, blood withdrawn and tested for coagulation *in vitro* clots in the normal period. A further factor in prolonging the bleeding is found in the failure of the blood clot to retract.

Hæmatologists are not yet agreed as to the mode of origin and of destruction of the blood platelets, or even that they exist as cellular entities, and consequently there is no definite knowledge of the cause of thrombocytopenia. (One view is that the actual production of platelets is unaffected but that the normal platelets are destroyed in excessive numbers by the spleen.)

Another important but little-understood feature of the disease is an increased permeability of the capillary walls, which are liable to rupture with undue ease. This may be clearly demonstrated by the test of Hess and Fränk, which consists in applying to the arm a tourniquet or sphygmomanometer band. When the pressure is gradually increased to obstruct the veins, a crop of purpuric spots will rapidly develop, both under and distal to the tourniquet.

It must be remembered that in many of these cases there are only mild recurrent attacks. Splenectomy is indicated in severe cases where there is actual risk to life from hæmorrhage, and is more likely to be successful in chronic than acute cases, in which relapses are not uncommon. After splenectomy the platelet count rapidly increases to normal, the bleeding diminishes and hæmorrhages cease.

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CHAPTER XXX

DISEASES OF THE ADRENAL GLANDS

LIKE the pituitary, the adrenal glands are composed of two distinct tissues, the medulla ectodermal, the cortex mesodermal—with corresponding functions.

The medulla is intimately related to the autonomic nervous system. It is derived from neuro-ectoderm, and it acts, through the agency of its secretion adrenalin, upon the sympathetic nerve endings. Its tumours are of two types. The former are composed of adrenalin-secreting cells and are known as chromaffin-cell tumours: the latter are composed of nerve cells and their progenitors, and are known as neuroblastomata.

The cortex, on the other hand, is of mesodermal origin, and appears first in the embryo as a ridge close to the mesonephros (Wolffian body). It is composed principally of large cells rich in cholesterol, for which it is probably a storehouse. Its tumours are composed of cells of similar type. The cortex has functions essential to life, whose nature are not clearly understood, and its complete removal or destruction inevitably causes rapid death. It appears to influence secondary sexual characters, and in tumours of the cortex these are sometimes profoundly altered.

In addition the cortex has an influence on the metabolism of sodium and chloride, as witnessed in Addison's disease. In this condition exhibition of the synthetic active principle of the cortex, desoxycorticosterone acetate (D.O.C.A.), parenterally or by its implantation into the tissues is effective in controlling the constitutional effects.

TUMOURS OF THE ADRENAL MEDULLA

The cells of the adrenal medulla are derived from the elements of the primitive sympathetic chain, from which they migrate at an early stage of embryonic life. When mature, they assume the faculty of secreting adrenalin, and may be distinguished microscopically by the readiness with which they take on a brown coloration when treated with chromic acid salts, the reason for their designation as pheochromocytes or chromaffin cells.

Tumours of the adrenal medulla are of two types. In the one, the cells retain their affinity for chromates and their property of secreting adrenalin. In the other, they revert to the structure of nerve cells or the progenitors of nerve cells.

(1) **Chromaffin-cell Tumour (Pheochromocytoma).** This tumour may be benign and encapsuled, or it may be malignant, when it invades neighbouring tissues and may metastasize. In some cases the tumour gives rise to dangerous and even fatal effects whilst still small in

others, it attains large size. Microscopically, the cells are spheroidal or of low columnar shape, and may show an irregular acinar arrangement. Chemical assay of a freshly removed tumour demonstrates its high adrenalin content.

The chief interest of this tumour lies in its clinical effects, which are due to intermittent release of large quantities of adrenalin. The blood pressure is raised and the heart hypertrophied, while there may be attacks of acute hypertension with tachycardia. Pallor followed by flushings of the skin, and nervous manifestations with dyspnoea, suffocation, and sensations of constriction in the epigastrium may be noted. Glycosuria is a common feature. It is important to be aware that affected subjects are very liable to surgical shock, and are therefore poor subjects for operation. In some cases, post-operative pulmonary cedema has also been noted.

(2) **Nerve-cell Tumours.** These tumours may be highly malignant, and reproduce nerve cells in very immature form (neuroblastoma), or they may be benign and reproduce ganglion nerve cells of adult type (ganglioneuroma). Intermediate types may be recognized.

Neuroblastoma and ganglioneuroma are not limited to the adrenal medulla, but may arise from any part of the autonomic nervous system, for example, in the retroperitoneal tissues or in the mediastinum. Tumours similar to a neuroblastoma may originate also in the retina.

Neuroblastoma (Sympathicoblastoma). This tumour occurs in infancy or childhood. It is highly malignant, metastasizes early, and often leads to a fatal issue in the course of a few months. The tumour sometimes attains large size, but often is permanently small and may remain unrecognized even at autopsy, or be mistaken for a secondary nodule. It forms a soft fleshy mass, very prone to hæmorrhage and degeneration, and it tends to invade surrounding tissues and neighbouring organs—for instance, the liver or spleen. The kidney is not always invaded, even though indented and compressed.

Microscopically, the tumour closely resembles a sarcoma, and for this reason its true nature was not recognized until 1910 (J. H. Wright). It is now clear that the origin is from nerve tissue and it seems probable that most retroperitoneal tumours of infants previously described as round-cell sarcoma are of this nature. The cells are small, round or oval, with large hyperchromatic nuclei and scanty protoplasm, and sometimes arranged in rosettes. Interspersed between groups of the cells are ill-defined fibres, which have been identified by special staining reactions as axis-cylinder processes and neuroglial fibrils.

The *metastases* of adrenalin blastoma occur early and are often the first evidence of the disease. Dissemination occurs by direct invasion, by lymphatic channels and by the blood stream. There is a remarkable tendency to metastasize in the cranial bones near the orbit, and such growths are very apt to be mistaken for primary tumours. Metastases occur also in the liver, spleen, lungs, ribs, peritoneum and other tissues.

Two clinical types of the disease have been described according to the sites affected by metastases.

Pepper in 1901 described the type associated with his name. The tumour is usually situated in the right adrenal gland, and the charac-

teristic feature is the presence of metastases in the liver. This viscus becomes greatly enlarged, soft and hæmorrhagic, and may fill the greater part of the abdomen, completely overshadowing the primary growth. Hutchison described the type characterized by the liability to secondary growths in the orbit and neighbouring parts. The metastasis may displace the eyeball and destroy it. The cranial bones affected by the tumour develop feathery projections like the "sun-ray" spicules of periosteal sarcoma (*see* Fig. 255).

The two types are by no means distinct and it should be emphasized that in most cases there are multiple metastases in situations other than the liver and orbit. According to Frew, the growths spread by the lymph channels, and the particular form of metastasis depends to some



FIG. 255. Cephalic metastasis from a neuroblastoma of the adrenal gland. Note the large amount of new bone, arranged in spicules perpendicular to the calvaria.

(Museum of Royal College of Surgeons of Edinburgh.)

extent upon the different lymph drainage of the two adrenal glands. Lymph vessels from the left adrenal communicate with the aortic chain of lymph glands, and cells derived from a left-sided tumour may thus reach the thoracic duct and the cervical lymph vessels. The lymph drainage of the right adrenal gland lies in close relation to the liver, and consequently a right-sided tumour usually metastasizes to the liver. Frew also claimed that the orbital metastasis is commonly on the same side as the primary growth, an observation not confirmed by others.

Ganglioneuroma. This rare tumour is of particular interest on account of its ganglion cell structure, which in ordinary circumstances is incapable of division. The tumour may affect adults or children. Intermediate forms of tumour occur, having in different parts the characteristics of ganglioneuroma and of neuroblastoma (*see* p. 322).

Microscopically, there are numerous nerve ganglion cells which lie in groups separated by bundles of medullated and non-medullated nerve fibres.

TUMOURS OF THE ADRENAL CORTEX

Although the adrenal cortex is of mesodermal origin its tumours have a glandular structure and are described as adenoma or carcinoma. In the majority of cases the tumour is an adenoma, a benign encapsulated tumour. Less often, though mainly of adenomatous structure, it displays a locally invasive character and attaches itself to the kidneys and perinephric fascia. In some cases, finally, it assumes frankly malignant properties and gives rise to distant metastases.

Whatever the degree of malignancy of the tumour, its naked eye appearances are fairly characteristic. It forms a somewhat globular tumour, yellow in colour, and may attain considerable size. Often it contains cysts filled with clear or bloodstained fluid, and hæmorrhages within its substance are common. In general appearance it may closely resemble a "hypernephroma" of the kidney.

Microscopically, the cells resemble those of the normal adrenal cortex, but are arranged atypically. In some cases there is a considerable degree of anaplasia and the tumour may have the appearance of a sarcoma.

The effects of adrenal cortical tumours vary greatly; in approximately 50% the tumour is symptomless or gives rise merely to an aching pain in the loin; in the remainder it causes a remarkable series of effects on the general metabolism and secondary sexual characters; the "adreno-genital" syndrome. Similar effects also follow functional overactivity of the adrenal gland, and are believed to be due to the elaboration of a hormone or hormones by the cortex.

In general, a cortical tumour occurring in an adult man or an elderly woman is symptomless, whereas one in a child or a young woman gives rise to characteristic changes.

In a male child the striking feature is virilism. The changes associated with puberty develop early (pubertas præcox). The voice breaks, there is a growth of hair on the face, body and pubic region, the external genitalia become enlarged, and the psychical changes characteristic of puberty develop. If the tumour is untreated, a brief period of precocious manhood is followed by early senility and death.

Sometimes in a male child the most obvious feature is a remarkable muscular development—the "infant Hercules" type.

In a female child the tendency towards virilism is also apparent. Puberty develops precociously, but in most cases there is no menstruation. The skin becomes dry and coarse, the voice is low pitched. The clitoris may be hypertrophied.

In a young woman the effects of an adrenal cortical tumour are even more remarkable, for they develop rapidly and cause striking changes in external appearance, metabolism and mentality. A girl of pleasing appearance may be converted within a few months into an obese hag. In brief, the typical features are as follows:—

Adiposity develops rapidly, with increase of weight of perhaps 20-30 pounds in a few months. The face is full-cheeked and unsightly. Fat, deposited in large pads, over the scapula region gives an appearance of hump-back, whilst great increase in the omental fat leads to marked prominence of the abdomen. The rapid adiposity causes striæ to develop in the skin like the striæ gravidarum.

Hirsuties appears early. A beard develops, and a growth of hair appears on the chest, abdomen and limbs. The hair of the scalp becomes short and coarse, whilst the pubic hair assumes the male distribution. The skin, often the seat of acne, becomes coarse and dry and scaly.

The internal generative organs—uterus and ovaries—become atrophic. Amenorrhœa is the rule. The clitoris is hypertrophied. The breasts become flattened.

Hypertension is a constant feature—the systolic blood pressure may be raised to 200 mm. Hg. or higher—and this may cause headaches. Polyuria may occur as a secondary effect.

Cushing's Syndrome. The remarkable series of changes described above are not confined to cases of adrenal cortical tumour, but occur also in diffuse hyperplasia of the cortex, or even in cases in which the cortex appears normal.

Some of these are examples of Cushing's syndrome (*see* p. 291), in which over-activity of the adrenal cortex is related to a basophil adenoma of the pituitary gland. Whilst the exact nature of this relationship is still obscure, it seems most satisfactory to regard the basophil adenoma as the primary lesion, which in virtue of its hormone stimulates the adrenal cortex to over-activity and thus gives rise to the same effects as a primary growth of the adrenal cortex. Broster and Vines have shown that the potent cells of a cortical tumour contain fuchsinophil granules, and that similar fuchsinophil cells are present in increased numbers in the cortex in cases of Cushing's syndrome and in diffuse hyperplasia of the cortex. Thus there is direct evidence of cortical over-activity even though on naked eye examination the cortex shows no abnormality. Recent work indicates that the adreno-genital syndrome is associated with excessive production of the male hormone androsterone; and, by hormone assay, it is now possible to determine whether the pituitary or the adrenal is responsible (*see* p. 291).

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CHAPTER XXXI

DISEASES OF THE URINARY ORGANS

Development of Urinary Tract. In early intra-uterine life the urinary tract undergoes a complicated development. Three distinct sets of excretory apparatus appear in turn, the pronephros, the mesonephros and the metanephros. The first of these disappears completely after a very brief existence, but the second and third persist, in part and in entirety, to form almost the whole of the urinary as well as portions of the generative tracts.

As in lower members of the animal kingdom, the primitive excretory organs—the pronephros and the mesonephros—have a segmental distribution. When the embryo becomes segmented, in the third week

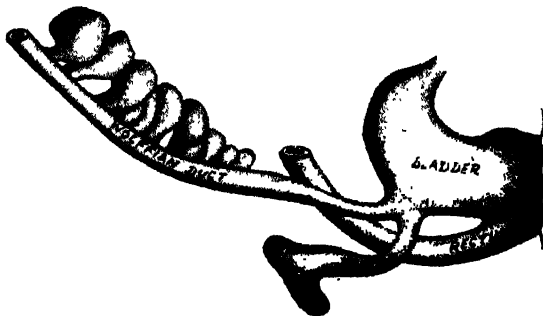


FIG. 256. Diagram showing development of genito-urinary tract.
(After Felix.)

of life, each segment receives an excretory apparatus, which is placed in a mesodermal mass, the intermediate cell mass, situated on the dorsal aspect of the body cavity. Each excretory apparatus consists of a few minute tubules opening into the body cavity. Those of the cephalad segments constitute the *pronephros*, and they disappear rapidly, leaving no trace; those situated nearer the hind part of the embryo, behind the mid-thoracic region, form the *mesonephros* (Wolffian body), and some of them persist. Each Wolffian body, which thus consists of a number of minute tubules embedded in mesoderm, projects forward into the coelom or body cavity, and forms a prominent longitudinal ridge lateral to the mid-line. At first all the tubules drain directly into the body cavity, but very soon there appears a long excretory channel, which lies in the substance of the Wolffian body, connects its different segments, and extends in a caudad direction as far as the cloaca. This

DISEASES OF THE URINARY ORGANS.

is the Wolffian duct, a structure of primary importance in the developing urinary tract (see also p. 658).

The kidney has a double origin, being derived partly from the Wolffian duct and partly from the *metanephros*, a mass of tissue situated at the hind end of the Wolffian body. The origin from the Wolffian duct takes the form of a small bud, which appears on the duct close to its orifice at the cloaca. This bud is the primitive ureter. It increases in length, becomes canalized, and eventually forms not only the ureter, but also the renal pelvis, the calyces and the straight collecting tubules of the kidney. As the "ureter bud" is developing, the metanephros appears and covers the growing end of the ureter by a cap of tissue, and eventually this "nephric cap" forms the remainder of the kidney, the glomeruli, the convoluted tubules and the loops of Henle. Thus each unit of the kidney is composed of two elements, metanephric and mesonephric, the one destined for the production of urine, the other for its elimination. At first these two elements are separate, but they unite at an early stage, and the continuity of each unit is established.

In the early stages of development the kidney lies at the level of the second sacral vertebra, and in close contact with its fellow of the opposite side, but it soon leaves the mid-line and passes towards the loin. At first the hilum of the kidney is directed forwards (ventrally), and the ureter and vessels enter on this aspect, but during its ascent to the loin the kidney rotates, so that the hilum assumes its adult position directed medially.

Congenital Malformations of Kidney and Ureter. As is to be expected from the complicated nature of their development, the kidney and ureter are subject to many varied malformations, some rare, others not uncommon. It will be convenient first to give a summary, necessarily brief, of the rarer anomalies, and to follow this by a detailed description of the more common and important types.

(1) *Failure in Development of One Kidney.* The growth of one kidney may be arrested at an early stage, so that although normally placed in the loin it is small and functionless. Such a kidney not infrequently possesses a dilated renal pelvis—one type of congenital hydronephrosis—and the kidney itself may be represented merely by a small cap of tissue perched on a large cystic cavity.

Less frequently the developmental failure occurs at an even earlier stage, before the appearance of the ureter-bud from the Wolffian duct, and there is a complete absence of kidney and ureter. In addition, the corresponding half of the trigone of the bladder is deformed, lacking its normal inter-ureteric bar, and the ureteral orifice is absent; the condition may therefore be recognized on cystoscopic examination.

(2) *Supernumerary Ureter or Kidney.* The ureter bud as it grows upwards from the Wolffian duct may bifurcate and form a Y-shaped ureter, or the bud may be double at its origin and form two complete ureters, which may lead into the two halves of a single kidney or into two separate kidneys. In this way arise varying degrees of duplicature of the ureter and kidney. Most often the ureter is single below, bifurcates higher up and ends in two renal pelves; sometimes there are

two complete ureters, and the kidney, too, may be double; in these cases the ureter from the superior renal pelvis enters the bladder at an orifice below and medial to the other.

(3) *Faulty Insertion of the Ureter.* By some error in the partition of the cloaca the lower end of the ureter may be displaced, and it may open into the prostatic urethra, or into the vagina, or more rarely into the rectum or even the seminal vesicle. The anomaly may give rise to the clinical paradox of incontinent micturition of half the urine combined with normal bladder control of the remainder.

(4) *Failure in Ascent of a Kidney.* This anomaly is rare apart from fusion, which is described below, but occasionally one kidney may be arrested in the pelvis, or in the iliac fossa, whilst its fellow ascends normally.

(5) *Fusion of the Kidneys.* In its primitive position at the level of the second sacral vertebra the kidney lies close to the mid-line and near its fellow, and the two may readily fuse. The commonest variety is "bilateral fusion" (horseshoe kidney), which is said to occur in approximately 1 of every 800 subjects, but rarely other types of fusion occur. The fused organs may fail to ascend from their pre-sacral origin (pelvic kidney), or they may ascend together to one loin (unilateral fusion), and other rare types are described.

Bilateral Fusion (Horseshoe Kidney). Here the kidneys lie on their respective sides of the mid-line, but are connected across the front of the aorta either by an isthmus of renal parenchyma or, more often, by a band of fibrous tissue. Usually the inferior extremities of the kidneys are connected, rarely the superior.

Anchorage of the kidney to its fellow prevents or perverts the normal process of ascent and rotation. Horseshoe kidneys are usually situated at a low level, with the connecting band in front of the promontory of the sacrum, and often the band is palpable. Since the normal rotation is interfered with, the hilum remains on the anterior aspect of the kidney and the renal pelvis points directly forwards, hence this condition may be recognized in a pyelogram, for the shadow of the renal pelvis is superimposed upon that of the calyces. The kidney is also tilted obliquely or may lie almost transversely, and the ureter, emerging anteriorly, passes down in front of its lower pole. Hydronephrosis is often present, and anomalies of blood supply are common.

As in all varieties of renal anomaly, there is an especial liability to infection and calculus-formation.

A *pelvic kidney*, a rare abnormality, lies in the retroperitoneal tissues in the pre-sacral region, where it forms a soft mass of irregular shape and variable size, hardly recognizable as renal tissue. Aberrant blood vessels supply it, derived from various neighbouring sources, and there is often some hydronephrosis. The ureters pursue a tortuous course before opening normally into the bladder. From its situation a pelvic kidney is apt to cause obstruction during labour, or it may, even more tragically, be mistaken for a pelvic neoplasm.

Unilateral fusion is a rare abnormality. One kidney is properly situated in the loin, correctly rotated and with normal ureter and

vessels, and to its lower pole is attached the other kidney. The displaced kidney carries across its own ureter, and its own artery, which cross the mid-line to their proper side of the bladder and aorta respectively. The translated kidney fails to rotate, so that its hilum and renal pelvis are directed forwards or even laterally.

(6) *Other anomalies* of the kidney and ureter include congenital stricture of the ureter, congenital hydronephrosis, and polycystic disease. These conditions will be described separately below.



FIG. 257. Polycystic disease of the kidney. The kidney is greatly enlarged and is replaced by cysts of various sizes. Some of the cysts contained clear watery fluid, others a viscid material which clotted on fixation in formalin. The renal pelvis and ureter are of small calibre. The renal arteries are abnormally placed.

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POLYCYSTIC DISEASE OF THE KIDNEYS

This is a disease of developmental origin but it is usually not manifest until early middle life. There is sometimes a definite familial incidence, and Cairns has reported a striking example in which three successive generations of a family were subjects of the disease.

Numerous cysts, small and large, appear in the substance of the kidneys, replacing the renal parenchyma and projecting like bunches of grapes under the capsule. When the condition is fully developed both kidneys are enlarged in greater or less degree, sometimes measuring as much as 25 cm. in the long axes. On cross

section it is seen that almost the whole renal substance is occupied by the cysts, and the remaining traces of parenchyma are compressed and fibrous. The cysts may project towards the renal pelvis as well as on the surface of the kidney. There is usually little or no dilatation of the pelvis, but sometimes hydronephrosis of the pelvic type exists. More commonly the renal pelvis, though not dilated, is stretched out by the increase in size of the whole kidney, so that the major calyces are elongated and the minor calyces, though of normal shape, are far apart.

The contents of the cysts may be thin and watery, or viscid. Some-

times the fluid is clear, of straw colour, containing albumen, urea, and various salts, but not infrequently it is discoloured by old or recent hæmorrhages to various shades of brown and red. The cyst walls are composed of cirrhotic renal tissue and are usually lined by flattened or columnar epithelial cells. The epithelium may proliferate, forming a lining several cells deep or with intracystic projections giving a semblance of a tumour not unlike that in an ovarian cyst.

The theory generally held at present attributes polycystic disease to a failure of union of the active "secreting" tubules and the passive conducting tubules of the kidney. The whole extent of the active tubules, including glomeruli, convolutions and loops of Henle, is derived from the metanephros, and these elements are at first entirely separate from the straight collecting tubules, which grow upwards from the ureter bud (*see* p. 608). In normal circumstances the two elements unite, but it is thought that incomplete or faulty union may lead to dilatation of the affected tubules.

The features of the disease are of interest in the light of its pathology. Polycystic disease may arise *in utero*, and the fetal kidneys may enlarge so greatly as to obstruct the course of labour, but, apart from this truly congenital variety, the disease rarely becomes manifest until the fourth or fifth decades. During the first thirty or forty years of life there may be no symptoms or signs of renal disease, but when at last the disease becomes manifest it often runs a rapid course. The earliest signs may be those of renal failure, anorexia, headache, indefinite gastric disturbances; sometimes the weight of the kidneys causes dragging pain in the abdomen, and their enlargement may attract attention; or there may be sudden hæmaturia. Uræmic manifestations lead to a fatal termination. The disease may be complicated in rare cases by infection, by the rupture of one of the cysts, or, exceptionally, by tumour formation.

Other Multiple Cysts in the Kidney. Small multiple cysts ("retention" cysts) form a constant feature of the granular contracted kidneys of chronic interstitial nephritis, and occasionally one or more of these may grow to large size, and give rise to a palpable swelling in the abdomen. Hydatid cysts may arise in the kidneys, and cysts may occur in relation to new growths in the kidneys.

SOLITARY CYSTS IN THE KIDNEY

The solitary or "serous" cyst of the kidney is of some rarity, but interesting because it may form a symptomless abdominal swelling whose nature is difficult to define. The condition is one of adult life, the average age incidence being forty-five years. The cyst usually projects from the lower pole of the kidney, and it may reach large dimensions. Often it grows with some rapidity and attains the size of an orange in the course of a few months.

With increase in size it gradually becomes pedunculated and it may eventually be freely mobile upon the surface of the kidney. Its wall is composed of fibrous tissue, often thin and translucent and contains

clear amber fluid, in which traces of albumen and urea may be found. A lining membrane of flattened or cubical cells may be present, but is usually incomplete. The cyst does not communicate with the renal pelvis or calyces, and for that reason pyelography may be unhelpful.

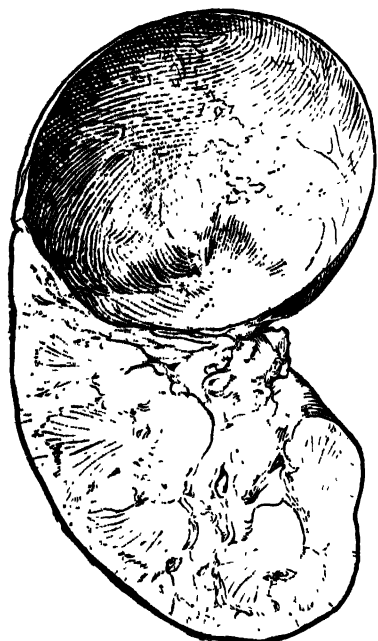


FIG. 258. Solitary cyst of the kidney.

(Museum of Royal College of Surgeons of Edinburgh.)

The cause of solitary cysts has hitherto been in doubt, and they have generally been regarded either as retention cysts from a localized form of chronic nephritis or as congenital lesions comparable to polycystic disease. The experimental work of Hinman and of Hepler, however, has suggested that cyst formation depends upon two essential features: (1) obstruction of some of the renal tubules, and (2) impairment of the blood supply to a limited area of the renal cortex.

HYDRONEPHROSIS AND HYDRO-URETER

Ætiology

Hydronephrosis with dilatation of the renal pelvis and calyces is due to obstruction of the outflow of urine. The obstruction may occur in any part of the urinary tract, as in the ureter by impaction of a stone or an intra-ureteral tumour or by pressure from an extraneous swelling. Obstruction may occur at the ureteral orifice in the bladder from cicatrization or tumour, or in the urethra when the bladder participates in the subsequent changes, and the condition is bilateral.

Should the obstruction to the outflow be complete and sudden, as in blockage of the ureter by an impacted calculus, kidney function is permanently arrested, the ureter proximally and the renal pelvis may remain normal or be attenuated and the hydronephrosis never reaches great size. But, when obstruction is discontinuous or only partial, as from ureteral stricture, prostatic enlargement or urethral stricture, the sequence of pathological events is exactly what takes place in other tubular viscera under similar circumstances, viz., utilisation of reserve muscular power with consequent hypertrophy followed by dilatation. In the bladder this is evidenced by thickening of its walls, increased trabeculation, and possibly formation of diverticula. In the ureter the walls become thickened, the lumen irregularly distended and the tube elongated and tortuous (hydro-ureter). The hypertrophy is less obvious in the renal pelvis and calyces. The pressure of recurrent accumulation of urine in the

minor calyces produces flattening of the renal papillæ, interference with the outflow from the tubules, and so back-pressure on the glomeruli. There is coincident interstitial nephritis and the essential structures undergo atrophy, partly from pressure, and partly from interference with the blood supply as the newly formed fibrous tissue in the kidney contracts; but gradually the kidney becomes distended and may reach a very large size, and, then, in its wall renal tissue cannot be recognized by the naked eye, and only in parts on microscopic examination. At any stage of this process, relief of the recurrent obstruction may arrest the progress of the hydronephrosis, but restoration of normal structure and functions in the kidney does not occur.

Experimental Observations. Experimental studies have afforded valuable information in regard to the mode of development of hydronephrosis and to the ensuing alterations in urinary secretion in the kidneys.

When one ureter is obstructed experimentally in rabbits for less than a fortnight the kidney will recover after removal of the obstruction; but if obstruction is maintained for three weeks the kidney atrophies, as its fellow hypertrophies, and there is no stimulus for the obstructed kidney to resume its function after release of the obstruction. If, however, at the time of release of the obstruction the other kidney is removed, the obstructed one responds to the needs of the body and resumes its full function. The conclusion drawn from the above experimental findings is that once the secretion of one kidney is seriously impaired the opposite one, provided it is healthy, undergoes hypertrophy and assumes the function of the obstructed kidney—"renal counterbalance." But what seems of even greater practical importance is the observation that once hypertrophy has occurred and increased function has been assumed the kidney retains it, and the obstructed or diseased kidney, its function impaired or lost, undergoes permanent atrophy; moreover it appears that obstruction affecting a kidney for more than a fortnight is likely to impair the function of that kidney.

Experiment suggests that increase of pressure in the renal pelvis has a decided influence on the renal circulation, both arterial and venous. First, the veins are obstructed and the kidney is congested, and to compensate for this the arterial pressure rises. Finally, the arteries become compressed and are gradually obliterated. This change occurs first at the cortex and extends progressively to the pelvis. When the blood flow through the glomeruli is slowed down, filtration diminishes and a smaller amount of urine is excreted.

According to the findings of Morison the obstructed contents of a hydronephrosis do not pass into stasis, but by a process of interchange continue in a state of circulation. In the first two days of obstruction, the fluid in the hydronephrotic sac is absorbed by the lymph vessels of the ureter and the renal pelvis. Subsequently it is absorbed by the convoluted tubules of the peripheral glomeruli, and later, as these tubules undergo pressure atrophy, by the subjacent tubules. Formerly it was supposed that absorption occurred directly *via* the veins—

"pyelo-venous backflow"; but it is now known that this only occurs when pressure within the renal pelvis is sufficient to injure the vein walls.

Varieties of Hydronephrosis and Hydro-ureter

Hydronephrosis and hydro-ureter may be congenital or acquired. In many cases there is an obvious cause of obstruction but in some it cannot be demonstrated.

Congenital Hydronephrosis and Hydro-ureter. Congenital hydronephrosis may result in enormous dilatation of the kidney, and this may be bilateral, and is then usually incompatible with life. Hydro-nephrosis is sometimes found in association with congenital abnormalities, such as horse-shoe kidney, unilateral fused kidney, and double ureter, and in the last example the hydronephrosis is frequently confined to the pelvis and calyces drained by one of the ureters. Congenital abnormalities of the ureter, such as valvular folds of mucous membrane or stenosis of a segment, may be responsible for hydronephrosis.

Congenital hydro-ureter is rare, it is nearly always bilateral and affects male subjects. It may become manifest in the first few days of life, because it is noticed the child passes little or no urine; but often the condition produces few effects until later childhood. The hydro-ureter is due to obstruction at the bladder neck in the posterior urethra, either from a disorder of the neuro-muscular mechanism controlling the urethro-vesical sphincter, or to a valvular fold of mucous membrane immediately distal to the orifices of the ejaculatory ducts. The ureters are thin walled, enormously dilated and tortuous (the left usually greater than the right), while the kidneys are hardly affected at all, and in their normal colour and size form a striking contrast to the intestine-like renal pelves and ureters. The bladder is greatly hypertrophied, and as a result of the paralytic state of the ureters reflux of urine occurs by gravitation or by contractions of the bladder. The disease may lead to dwarfism, chronic nephritis and delayed rickets. Death may occur from uræmia or from pyelo-nephritis.

Hydronephrosis and Hydro-ureter in Pregnancy. Dilatation of the ureters, and to a less extent of the renal pelvis is a normal occurrence in pregnancy. The dilatation usually affects the right ureter alone, and is always less on the left than on the right, possibly owing to the normal deflexion of the uterus to that side. Ureteral dilatation begins about the tenth week and increases progressively as pregnancy advances.

Histological examination of the ureter in pregnancy shows that its muscle and fibrous tissue, especially in the lower portion, undergo hypertrophy similar to that of the tissues of the uterus. When pregnancy is ended the ureter usually returns to normal, but in a few instances dilatation remains.

The cause of the ureteral dilatation in pregnancy has not been fully determined: pressure may be a contributory factor, but of greater importance is neurogenic obstruction at the lower end of the ureter comparable to achalasia in other organs.

The obstruction at the lower end of the ureter and the resulting stasis of urine probably account for the frequency of *bacillus coli* infection. Apart from infection, the tension within the dilated ureter may be responsible for attacks like renal colic, or, by its effects of increasing the vascular tension in the kidneys, for attacks of hæmaturia.

Hydronephrosis and Hydro-ureter with Obvious Cause of Obstruction. Obstructing lesions which may give rise to unilateral hydronephrosis include stones in the kidney or ureter, stricture of the ureter, inflammatory peri-ureteritis, and, rarely, tumours of the renal pelvis or of the ureter. Bilateral hydronephrosis may arise from urethral obstruction due to stricture or to prostatic enlargement, from paralytic dilatation of the bladder, from long-continued prolapse of the uterus, or from inflammatory infiltration of the broad ligaments. A calculus in the renal pelvis may cause intermittent obstruction at the pelvi-ureteral junction, and this is especially apt to occur when the stone is of small size. Large branched calculi, on the other hand, are not usual in hydronephrosis. Calculi associated with hydronephrosis usually remain small, as their growth is retarded as a result of the diminished amount of crystal-forming material in the urine.

Calculi in the ureter may lead to hydronephrosis if the calculus gives rise to sufficient obstruction to raise the tension in the renal pelvis. The first noticeable change is in the renal pelvis and the calyces, but later the ureter above the stone becomes dilated and may reach the diameter of the thumb. Even minute calculi may give rise to sufficient obstruction to cause hydronephrosis.

Hydronephrosis and Hydro-ureter without Obvious Cause of Obstruction. This form of hydronephrosis is usually unilateral. It is very rare in infancy and it is usually found in subjects between twenty and forty years, although it may be much later before it comes under notice. It generally develops insidiously, and it may reach large size without obvious effects. When the kidney is examined at operation no cause for the hydronephrosis can usually be discovered; such cases constitute the majority of examples of hydronephrosis, and receive the non-committal designation *idiopathic hydronephrosis*. It has been suggested that the underlying cause is long-continued faulty emptying of the renal pelvis due to inco-ordination of the neuro-muscular mechanism of the renal pelvis and the ureter. This explanation lacks full confirmation, but it seems to be the only one which accounts for the obstruction which precedes the dilatation.

Unilateral hydro-ureter—megalo-ureter—with or without hydronephrosis, is sometimes present without demonstrable cause. The whole ureter is usually dilated, except the intra-vesical portion which is normal. The ureter is elongated and thick walled due to overgrowth of the circular muscle coat. The condition is believed to be the counterpart of megacolon and is probably due to disturbance of the sympathetic innervation of the distal end of the ureter resulting in exaggerated tonicity of the uretero-vesical sphincter.

Aberrant Renal Vessels in relation to Hydronephrosis. Pressure caused by abnormal renal vessels has often been blamed for the onset of hydronephrosis. At the hilum of the kidney the renal artery divides

into three branches—two superior and one inferior. The inferior branch varies in its point of origin from the main stem; it may leave the parent vessel at any point between the aorta and the hilum of the kidney, or it may even come directly from the aorta. When the inferior vessel is abnormally situated it is in more intimate contact with the renal pelvis or with the ureter, and at its point of contact with these structures there may be fibrous thickening around the vessel. Hydro-



FIG. 259. Hydronephrosis. The renal pelvis is greatly dilated and the kidney is enlarged. On section, the calyces were found to be dilated, but to a relatively small degree, and a considerable amount of secretory tissue remained. The ureter is of small calibre. No cause for the hydronephrosis was found. An abnormally placed artery passed close to the pelvi-ureteral junction to reach the inferior extremity of the kidney.

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nephrosis is sometimes found in association with such an abnormal vessel, and it is difficult or impossible to say whether the vessel is responsible for obstruction or not. It seems most likely that the vessel is implicated only after the pelvis dilates.

Abnormal Renal Mobility and Hydronephrosis. Abnormal mobility of the kidney has been suggested as a common cause of hydronephrosis on account of the intermittent ureteral obstruction to which it may give rise. Pyelographic examination has shown, however, that hydronephrosis seldom develops, even in cases of long standing abnormal renal mobility. Experimentally, Tuffier was unable to produce hydronephrosis in animals by separating the kidney and ureter from their

attachments, and hydronephrosis did not develop, even when the ureter was looped upon itself.

Morbid Anatomy

In the early stages of hydronephrosis the capacity of the pelvis of the kidney is increased but the kidney shows little change beyond slight flattening of the renal papillæ. The early changes are portrayed in a radiogram after injection of opaque media; the resulting pyelogram shows dilatation of the renal pelvis, broadening of the major calyces and loss of the "cupping" of the minor calyces (see Fig. 260).

As the renal pelvis dilates the pelvi-ureteral junction may no longer be situated at the lowest part of the pelvis, and a valve-like spur may develop between the dependent part of the pelvis and the ureter.

The ultimate form assumed by the hydronephrosis depends upon the normal relationship of the renal pelvis to the kidney substance. When most of the renal pelvis is situated outside the kidney (extra-renal type), the pelvis, less resistant than the kidney, dilates. From increased tension and forms a more or less spherical fibrous sac on which rests the remains of the kidney. The kidney atrophies progressively and may finally be unrecognizable. When the pelvis is mostly enveloped by the kidney (renal type), dilatation occurs within the kidney and the major and minor calyces gradually enlarge at the expense of the kidney substance, which becomes compressed and thinned out over their surface, so that a multiloculated sac, which retains the shape of the kidney, is formed. Intermediate types may occur, depending on anatomical variations in the relationship of the kidney to its pelvis.

As a hydronephrotic kidney increases in size it does so in the direction of least resistance, therefore it projects towards the peritoneum, which forms an investment for its anterior surface. On the right side it tends to displace the hepatic flexure downwards and medially, but on the left side the splenic flexure maintains its attachment to the parietes. It is very exceptional for a hydronephrosis to exert harmful pressure on the abdominal organs.

A hydronephrosis is said to be "open" when urine escapes from it and "closed" when the outflow ceases. An open hydronephrosis is liable to become completely obstructed from time to time. This may be determined by the intake of large draughts of fluid and it



FIG. 260. Pyelogram of right-sided hydronephrosis. The pelvis and all the calyces are greatly dilated. Note the characteristic broadening and clubbing of the calyces.

may give rise to attacks of pain in the loin and enlargement of the kidney.

At cystoscopic examination it is often noted that the hydronephrotic kidney secretes more copiously than the healthy one, as is evidenced by more frequent ureteral contractions, but the urine is more dilute. In more advanced cases the escape of urine may be very infrequent, and when obstruction is absolute ureteral contractions cease. When a ureteral catheter is passed large quantities of urine are often withdrawn, and on injecting fluid into the renal pelvis its capacity may be found to be greatly increased. In a large hydronephrosis the opaque fluid injected for diagnostic purposes may be so greatly diluted by the fluid contents of the sac that no shadow may be portrayed radiographically.

A hydronephrotic kidney on account of its size is more liable to injury than a normal one. Spontaneous rupture is recorded.

STRICTURE OF THE URETER

Stenosis of the ureter may be of congenital origin or it may be an acquired condition due to pathological processes affecting its walls.

Congenital stenosis is relatively uncommon, and autopsy examination of 1,200 infants by Englisch (in Vienna) showed that it was present in 65 cases; the stenosis was situated at the upper end of the ureter in 34, at the lower end in 28, and about the middle of the ureter in 3. The stenosis may be due to persistence of a valve or fold of mucous membrane or to narrowing of a segment of the ureter. Any part of the ureter may be affected, but the commonest situations for such abnormalities are at the upper end, at the entrance to the bladder and at the point at which the ureter enters the pelvis minor. The degree of ureteral obstruction is very variable, but in some it is sufficient to lead to hydronephrosis.

Acquired strictures of the ureter are very rare. They may result from cicatrization of an ulcer caused by an impacted calculus, from injury at operation, and from the infiltration of the ureteral wall by a malignant tumour of the colon or of the female pelvic organs. Occasionally ureteral strictures are found in association with long-standing infection of the lower urinary tract, especially in association with urethral stricture. Strictures of the ureter have been observed after childbirth (so-called puerperal strictures). They are commonest on the right side and in the pelvic portion of the ureter near its termination in the bladder. They are believed to result from injury to the wall of the ureter in parturition, with subsequent repair by scar tissue. The hydro-ureter of pregnancy predisposes to their formation (*see* p. 614).

The ureter at the site of a stricture is indurated by scar tissue. Usually all coats are involved and the muscle is replaced by fibrous tissue. Periureteral fibrosis may fix the ureter to the peritoneum. The lumen of the ureter at the stricture is reduced and its epithelium is often of a squamous character.

The ureter above the stricture is dilated and slightly hypertrophied and may be tortuous. Stricture of the ureter tends to cause obstruction of urinary outflow and hydronephrosis, and the stagnation of urine renders the kidney more vulnerable to infection, especially by *Bacillus coli*, so that pyelitis is a common complication.

Ureterocele. Ureterocele or ballooning of the intravesical portion of the ureter into the bladder is a rare condition. The most important predisposing cause is narrowing of the ureteral orifice of either congenital or acquired origin. The prolapse may lead to interference with renal drainage. In the advanced stages the ureterocele sac may be very large and may cause blockage of the urethra during micturition. In women it may traverse the urethra and present at the vulva and give rise to incontinence.

PYOGENIC INFECTION OF THE KIDNEYS

The principal pyogenic infections of the kidney of surgical importance are: (1) Pyelitis, in which the inflammation is chiefly restricted to the mucous membrane of the renal pelvis. (2) Pyelonephritis, in which the inflammation involves both the renal pelvis and the parenchyma of the kidney. (3) Pyonephrosis, in which there is an added factor of obstruction to the outflow of urine, and (4) Hæmatogenous suppurative nephritis.

Pyelitis

This is a common infection. It affects women far more often than men, and it is especially common

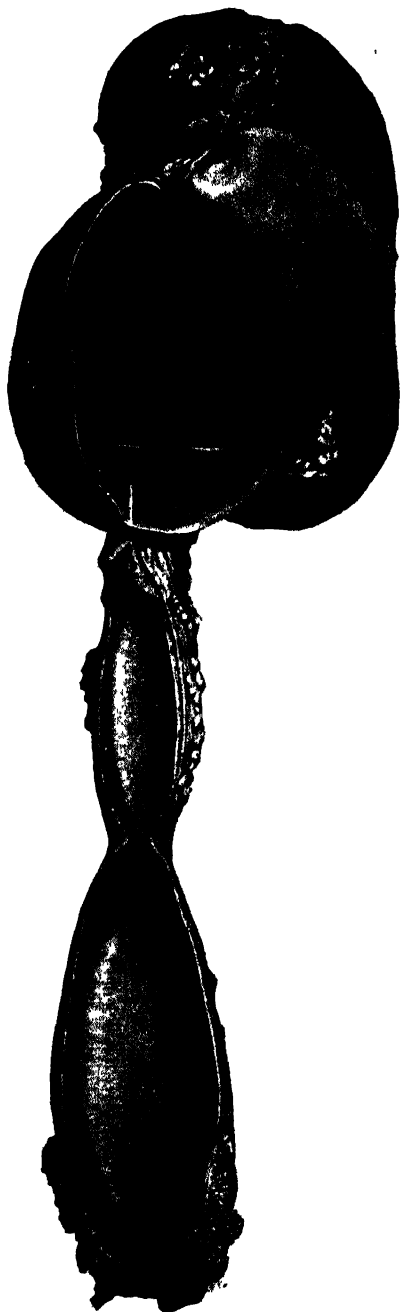


FIG. 261. Hydronephrosis and hydro-ureter due to a fibrous stricture at the lower end of the ureter.

(By courtesy of the late Mr. D. S. Middleton.)

as a complication of pregnancy. In the great majority of cases it affects the right kidney.

Pyelitis may arise acutely and after a short period may undergo resolution, or it may arise insidiously and pursue a chronic course.

Acute pyelitis is often sudden in onset and may be accompanied by severe constitutional disturbance with high temperature, rigors and vomiting. Since the urine is highly acid it may give rise to scalding pain on micturition.

The pathological state is not fully understood, since for obvious reasons the opportunity rarely offers of examining a kidney in a state of simple pyelitis. It is presumed, however, that there is an inflammatory reaction which is mainly evident in the mucous membrane of the renal pelvis. Probably in all cases the renal parenchyma shares, to a limited extent, in the pathological changes.

Chronic pyelitis may arise insidiously or may occur as a sequel to acute pyelitis. It is a common condition, and may be responsible for much chronic disability associated with pain over the affected kidney and frequency of micturition. The pathological changes are those of a chronic inflammation. The mucous membrane of the renal pelvis is thickened and somewhat pale in colour, or in some cases it is thin and atrophic. The muscle coat of the renal pelvis and ureter is atrophic, and this change may lead to mild degrees of hydronephrosis, sometimes accompanied by dilatation of the ureter.

In some cases in response to the chronic irritation the mucous membrane of the renal pelvis undergoes proliferative changes and assumes a squamous-cell character—*leukoplakia of the renal pelvis*. This change, which is distinctly rare, has sometimes been found in kidneys containing calculi, presumably the result of the chronic irritation. Leukoplakia of the renal pelvis is regarded by some as a pre-cancerous lesion.

Ætiology of Pyelitis. The infecting organism in pyelitis is generally a coliform bacillus, but the factors that determine its localization in the renal pelvis are not yet definitely established. It is well known that an apparently healthy kidney may allow organisms to pass from the blood stream into the urine, and it is established that *B. coli* is often "excreted" in this way. It seems probable, therefore, that in pyelitis the infection is hæmatogenous, and that the determining factor is some local lesion which renders the renal pelvis unduly susceptible. Occasionally there is some obvious local lesion such as a stone or a malformation of the kidney. In pregnancy pressure upon the right ureter by the enlarging uterus, or hydro-ureter from other causes (see p. 614), may, as a result of urinary stasis, predispose to pyelitis.

Whilst the view generally held is that given above, it must be admitted as a possibility that the organisms are derived from the colon and reach the kidney directly or by way of the lymph vessels. Such a theory would also explain the frequency of pyelitis in women, who are especially liable to colon sepsis, and in the right kidney, which lies so closely related to the proximal colon.

Pyelonephritis

Here the infection attacks the renal parenchyma as well as the mucous membrane of the pelvis. The disease may be unilateral or bilateral, depending upon its manner of causation, and, in either case, it is considerably more serious than pyelitis. Clinically, it is associated with a high temperature, rigors, and great toxæmia; and often it leads to uræmia and ends fatally.

The kidney becomes swollen, engorged with blood and of a purple colour. At first, the inflammatory change is most obvious in the mucous membrane of the pelvis and calyces, which are intensely hyperæmic and œdematous. Later, small abscesses appear in the parenchyma of the kidney, first near one extremity of the organ, later in other parts. Extending from the pelvis to the cortex there are numerous faint greyish-yellow streaks of suppuration which mark the spread of infection between the tubules of the medulla towards the capsule. Later, the abscesses increase in size and may become confluent or open at the renal pelvis, or they may spread towards the surface of the kidney and lead to suppuration in the perinephric tissues.

Ætiology. The infecting organisms in pyelonephritis are generally mixed. Coliform bacilli are often present along with staphylococci, streptococci, and sometimes *B. proteus* and other organisms. In some cases the infection appears to be hæmatogenous, and its onset may be determined by pre-existing disease of the kidney, for example, by nephrolithiasis or a tumour. In such circumstances pyelonephritis may be unilateral, though it is very apt to become bilateral. In the majority of cases, however, the infection is derived from the lower urinary tract, whence it reaches the kidney, along the ureter or, more probably, by way of the peri-ureteral lymph vessels. This ascending type of infection generally follows septic cystitis (*consecutive suppurative nephritis*), and is especially apt to occur when there is an obstruction to the outflow of urine, for example, by enlargement of the prostate or by stricture of the urethra. Such an obstruction affects both kidneys, and consequently pyelonephritis of this type is generally bilateral. The ascending infection is especially apt to follow operations on the bladder, even the passage of instruments.

Pyonephrosis

In this condition there is an infection of the kidney and renal pelvis, and, in addition, a partial or complete obstruction to the outflow of urine. Pyonephrosis is to be distinguished from infection of a pre-existing hydronephrosis, though in the later stages the two conditions are somewhat similar.

The infection in pyonephrosis is generally mixed. Coliform bacilli usually predominate, and give the pus a characteristic odour, and staphylococci, streptococci and *B. proteus* are often present.

The obstructing agent usually is a stone (*calculous pyonephrosis*) or less often a tumour of the kidney or renal pelvis. The stone is often of large size, filling the renal pelvis. In other cases a small stone is responsible, by obstructing the ureter or the pelvi-ureteral junction. Occa-

sionally a stone obstructing one of the major calyces gives rise to pyonephrosis limited to one part of the kidney.

As a result of the infection the mucous membrane of the pelvis and calyces becomes inflamed and ulcerated. The parenchyma of the kidney becomes thinned by pressure and necrosis. Such parenchyma as remains is infiltrated by inflammatory products and often riddled with small abscesses. The pelvis and calyces are greatly dilated, and contain pus mixed with alkaline, ammoniacal urine. Often there are secondary phosphate concretions.

The renal pelvis is generally dilated, but rarely to the same extent as in hydronephrosis, for the thick, inflamed wall resists distension.

Usually the obstruction to the outflow from the kidney is not complete, and consequently the urine contains quantities of pus and is generally foul smelling. Complete obstruction may supervene, however, and then the pyuria becomes less obvious, and coincidentally the kidney becomes larger and more tender, and the constitutional effects become aggravated.

Hæmatogenous Suppurative Nephritis

In septicæmia and in pyæmia multiple small abscesses may develop in the kidney. They vary in size from a pin's head to a cherry. They are usually situated in the renal cortex.

(Staphylococcal infection of the kidney is an occasional complication of such lesions as furunculosis, carbuncle and osteomyelitis. It occurs in adults and is nearly always unilateral, and, in a number of cases, is preceded by trauma to the kidney. The resulting lesion may take the form of an acute abscess in the cortex, but more often the suppurative process is subacute and is associated with multiple areas of necrosis—which if aggregated form the *carbuncle of the kidney*. In the early stages there are multiple opaque foci in one part of the cortex, later these may fuse and give rise to a localized enlargement of the kidney. A perinephric abscess results from the outward extension of the suppurative process, but eruption into the renal pelvis is exceptional.

This form of renal infection pursues a subacute course; it is attended by rigors, sweating, and pain in the loin, and there may be considerable emaciation. Urinary symptoms are generally absent, and as the inflammatory process begins in the cortex of the kidney and remains confined to it, pus and organisms are not found in the urine. A perinephric abscess may be the most obvious feature and then the renal origin of the infection is often overlooked or it is not suspected.

TUBERCULOSIS OF THE URINARY TRACT

Tuberculous infection of the urinary tract is a local manifestation in a tuberculous subject, the result of a systemic infection. The primary source of infection, which may be active or quiescent, is either in the lung or less often a lymph gland. Evidence, or a history of tuberculous disease elsewhere is forthcoming in at least 75% of cases, and, in the

male sex, genital tuberculosis affecting the epididymis is present with considerable frequency.

The primary lesion in the urinary tract is almost invariably situated in one kidney, and since there is usually no evidence of hæmatogenous infection in other organs, it is generally presumed to be due to a solitary embolus of tubercle bacilli set free in the blood stream. It seems possible, however, that, in some cases at least, the renal lesion is due to the lighting-up of a latent miliary focus.

Once established in the kidney, the disease tends to spread throughout the urinary tract, and eventually, if unchecked, involves the ureter, the bladder, and the remaining kidney. The mode of spread of tuberculosis in the urinary tract has been the subject of much speculation. It seems almost certain that the disease spreads from the kidney down the ureter to the bladder by direct continuity of tissue along the mucous membrane, and also in the peri-ureteral lymph vessels. It has been suggested that the bladder may be infected by organisms carried down in the urine, but this seems unlikely. The remaining kidney may be involved by further hæmatogenous infection, or by infection ascending from the bladder. Such an ascending infection may be conceived to occur by direct spread along the mucous membrane of the ureter, by way of the peri-ureteral lymphatics, or possibly even as a result of regurgitation of infected urine from the contracted bladder. In most cases it seems likely that spread by continuity of tissue is responsible.

Tuberculosis of the Kidney

Excluding acute miliary lesions, renal tuberculosis takes a chronic course. Although hæmatogenous, it is almost always confined at first to one kidney, and probably in about 80% it remains unilateral for several months, or even years.

The earliest focus lies in the cortex, near one or other extremity of the kidney, rarely at its mid-part. By extension and ulceration the disease reaches the mucous membrane of a neighbouring calyx, whence it spreads to other parts of the renal pelvis. The renal parenchyma is invaded by tubercles, at first discrete, later confluent, and eventually the capsule is reached. Occasionally a cold abscess develops in the perinephric fat.

It is important to recognize that all the early changes occur principally within the substance of the kidney and that the disease may be advanced before there are notable changes in the urine or other pathological evidence of significance.

Gross Appearance. In most cases the kidney is widely involved. The perinephric fat is œdematous, matted and adherent, so that the kidney is exposed with some difficulty. There may be tiny tubercles under the capsule or the surface may be raised in large nodular protuberances, while the kidney feels indurated or soft and perhaps fluctuant.

On section of the extirpated kidney, the extent of the disease is seen to vary in different parts, being usually most advanced near the renal pelvis at one extremity (*see Fig. 262*). The pelvis is usually

ulcerated, and its wall replaced by granulation tissue. When the disease is extensive the parenchyma is partly replaced by cavities, which are lined by caseous matter and granulation tissue and contain thick white pus. Extending towards the cortex are yellow lines which indicate secondary pathways of extension, and scattered throughout the kidney there may be many discrete tubercles.



FIG. 262. Tuberculosis of the kidney. The kidney is greatly enlarged. There are several cavities lined with tuberculous granulation tissue, communicating with the renal pelvis, and all the calyces are affected by the ulcerative process. Numerous small tubercles are seen in the cortex and medulla, and in the mucous membrane of the renal pelvis.

(Department of Surgery, University of Edinburgh.)

The wall of the ureter may be thick, infiltrated with tubercles, and fibrotic, its epithelial surface ulcerated and rough. The lumen of the ureter is sometimes obliterated by fibrosis, but often is dilated, forming a thick-walled, irregularly tortuous tube.

Special Types of Lesion. In typical cases the progress of the disease is as described above, and the lesion may be designated *tuberculous pyelonephritis* (see Fig. 262). In other cases the progress is modified and other types of lesion may be recognized. If the ureter should become completely obstructed, and the disease is of mild type, the pelvis and calyces become dilated with turbid watery fluid—*tuberculous hydronephrosis*. Sometimes a slow caseous process spreads through the entire kidney, which becomes a functionless multilocular sac completely filled with

solid cheesy material—*tuberculous pyonephrosis* or *caseous kidney* (see Fig. 263). (In these cases the ureter is often occluded, but since all secreting tissue is already destroyed the pelvis is not dilated but remains small. At this stage the disease not uncommonly becomes arrested, bacilli disappear from the urine and the symptoms subside. Such a sequestered caseous mass often undergoes partial calcification, and on radiography casts a dense, irregularly mottled shadow.

Significance of "Tuberculous Bacilluria." It has often been

observed in the course of progressive tuberculosis of any part of the body that the urine contains tubercle bacilli, yet the kidney, subsequently examined at autopsy, appears unaffected, hence it has been inferred that the kidney may excrete tubercle bacilli, yet remain free from disease. The accuracy of this observation, however, has been rendered very doubtful by the extensive researches of Medlar, who showed that by careful search tubercles are always to be found in such kidneys, though sometimes only after prolonged examination of serial sections.

Nevertheless, the fact remains that the presence of bacilli in the urine is quite consistent with the absence of any gross lesion; an observation that emphasizes the difficulty of basing diagnosis solely on urinary examination.

Tuberculosis of the Bladder

Usually the bladder is infected from the kidney and ureter, less often from the seminal vesicles or the prostate.

When derived from the kidney, the vesical infection begins at the corresponding ureteral orifice, and spreads thence over the trigone, and ultimately to the fundus. The earliest sign is œdema of the lips of the ureteral orifice; in a short time this area becomes congested, and later small ulcers appear, which are shallow and hæmorrhagic, with adherent tags of blood clot and pus; eventually tubercles may be recognizable, though this is rare. Since the muscle of the ureteral wall is extensively involved it fails to contract during the passage of urine, and consequently one of the early signs visible on cystoscopy is the cessation of the normal rhythmical contraction and parting of the lips of the orifice. Later, cicatricial contraction of the ureter causes retraction of the corresponding corner of the trigone, and the orifice forms a gaping circular pit—the so-called golf-hole ureter.

As the disease progresses, the bladder wall becomes infiltrated with inflammatory exudate and cells; it becomes thickened, contracted and inelastic, and its capacity is reduced from the normal of 300 c.cm. to as low as 50 c.cm. As a secondary effect, a certain degree of "back pressure" may develop, and may lead to hydronephrosis. This complica-



FIG. 263. Caseous tuberculous of the kidney (tuberculous pyonephrosis). The renal pelvis is small and the ureter is occluded. The entire secretory tissue is replaced by large cavities containing caseous material.

(Department of Surgery, University of Edinburgh.)

tion, affecting the function of the second kidney, is naturally of serious import.

TUMOURS OF THE KIDNEY

Malignant tumours of the kidney belong to two principal classes : (1) the adenocarcinoma or hypernephroma, a tumour affecting adults and arising in the renal parenchyma ; (2) the adenosarcoma (mixed or embryonic tumour) of infants and young children.

Tumours arise also from the epithelial lining of the renal pelvis (*see* p. 631).

Adenocarcinoma ; Hypernephroma

Practically all malignant epithelial tumours arising in the renal parenchyma conform closely to one general type, of striking appearance, characteristic morphology, and uniform behaviour. They are bulky, irregularly lobulated tumours, which may be firm, solid and of grey or yellow colour, but often undergo softening, cyst formation, and discoloration by extravasated blood. They invade the kidney substance gradually, and show a great tendency to metastasize by the blood stream.

In the past, attempts have been made to distinguish in this group two varieties—*hypernephroma*, of adrenal origin, and *adenocarcinoma*, derived from the tubules of the kidney. The distinction has been made principally upon histological grounds, according as the tumour resembles the adrenal cortex or contains tubules and papillæ more suggestive of a renal origin. It seems probable, however, that this distinction has little foundation and should be discarded. Variations undoubtedly occur in different tumours, but they are variations of degree, and often the same tumour varies in different parts. The question is one of histology, and most histologists now follow Nicholson in regarding the tumours as renal adenocarcinoma (*see also* p. 628).

Tumours of this class affect men more often than women, usually between the ages of thirty and fifty years. They arise in the cortex and adjacent parts of the medulla, or rarely in one of the pyramids ; commonly at one extremity of the kidney, especially the upper one. At first the tumour is circumscribed and rounded, lying entirely within the renal parenchyma. With increase in size it encroaches upon and ulcerates into the calyces of the renal pelvis, and disseminates to distant sites. The unaffected portion of the kidney, dwarfed by comparison, is perched upon the tumour ; and the renal pelvis and calyces are deformed or obliterated (*see* Fig. 264). The tumour has an imperfect capsule of condensed renal tissue, and broad fibrous trabeculae subdivide it into numerous lobules. Near its centre the tumour is often solid, of firm consistence and bright yellow colour. Around this central core the tumour is partly solid, partly excavated by cyst-like spaces, some of which are bright yellow, whilst others are discoloured to various shades of orange and red.

Microscopic Appearance. This varies somewhat in different tumours

and in different parts of the same tumour, but the general picture is a fairly characteristic one. The cells superficially resemble those of the adrenal cortex, being cuboidal or columnar, though often modified in shape by mutual pressure. Their nuclei are small, rounded and deeply stained; their cytoplasm is abundant and either clear or slightly granular. In the fresh state, before being subjected to fat solvents, the



FIG. 264. Adenocarcinoma (hypernephroma) of the kidney. The tumour occupies the lower pole of the kidney and projects into the renal pelvis. There are numerous small cysts and areas of necrosis and hæmorrhage.

(*Department of Surgery, University of Edinburgh.*)

cells are filled with a soluble material containing glycogen, cholesterol, and fats. They are disposed in sheets or in long columns, or in solid masses, bounded by delicate trabeculæ or connective tissue. The columns of cells are intimately related to blood vessels, which are large and thin-walled. Generally, the cellular masses are solid, with no visible acini, but sometimes there are irregular spaces, tubular clefts or papillary formations.

Spread of the Tumour. The tumour progresses slowly at first, but finally it encroaches upon the calyces of the renal pelvis, and leads to hæmaturia. The quantity of blood lost is often considerable and clots may form in the renal pelvis, causing colicky pains during their descent within the ureter.

Tumours of the kidney have a remarkable tendency to spread along the lumen of the renal vein, which is sometimes choked by tumour tissue, and the growth may extend by continuity, even into the heart and lungs. Rarely a mass in the left renal vein obstructs the testicular vein and leads to a certain degree of varicocele and to pain in the testis.

Distant metastases develop most often in the lungs and in bones. Pain in the chest or hæmoptysis, or a pathological fracture due to a bone metastasis, may be the first indication of the malignant process. Not infrequently a single metastasis appears at a moderately early stage of the disease, some time before general dissemination occurs.

Nature of the Tumour. The nature of the tumour has been a much debated subject. Until comparatively recent years the field has been held



FIG. 265. Adenocarcinoma (hypernephroma) of the kidney. $\times 110$. The tumour is composed of solid masses of cells, with small, deeply staining nuclei and abundant clear protoplasm. Note the large thin-walled blood space.

(Laboratory of Royal College of Physicians of Edinburgh.)

by the theory of von Grawitz, who considered that the tumour is of adrenal origin—a hypernephroma—and that it arises from displaced portions of adrenal tissue within the substance of the kidney. This theory is based upon two principal considerations: (1) that “rests” of adrenal tissue are present sometimes under the capsule or in the cortex of the kidney, (2) that tumours of this type closely resemble adrenal tissue in their gross appearance, in their architecture, and in the characteristics of their individual cells.

Von Grawitz's theory has been assailed on numerous occasions, and Nicholson, in a masterly review of the whole subject, brought convincing evidence against it, which may be summarized as follows: (1) adrenal rests are not confined to the kidneys, but occur often in the broad ligaments, in the retroperitoneal tissues, and elsewhere, whereas “hypernephromata” are almost invariably intrarenal; (2) the architecture of these tumours is no indication of their origin, but results from

the mutual pressure of swollen hydropic cells; (3) the individual cells—with their content of glycogen and fat—though very like adrenal cells are not unlike cells in other situations; (4) true tumours of adrenal cortex, arising in the adrenal gland, almost always have a very obvious effect upon the secondary sexual characteristics, and lead to sexual precocity with virilism, whereas no such biological action has been observed in association with such a tumour in the kidney.

As a compromise between these opposing views, many attempts have been made to identify different types of tumour, some of adrenal, others of renal origin, but such a subdivision, as has already been pointed out, is beset by many difficulties, and has not been widely adopted. At present general opinion favours the view expressed by Nicholson, that the tumour is an adenocarcinoma derived from cells of the renal tubules.

Renal Adenosarcoma (Nephroblastoma; Embryoma)

This rare tumour occurs in childhood, practically never after the seventh year. It forms a rounded or nodular mass, which may attain great size, replacing the entire kidney, displacing the viscera and expanding the whole abdomen.

The tumour arises in the substance of the kidney and is of bluish-white or pale grey colour. The blood supply is poor, with scanty thin-walled vessels, and consequently the tumour is liable to undergo necrosis with hæmorrhages, zones of softening, and the formation of cyst-like cavities.

The tumour is not encapsuled, and it invades the renal parenchyma and destroys it, so that in the later stages little trace of normal tubules may remain. The ureter, when traced upwards, merges into the tumour mass. The renal pelvis is compressed and obliterated but its cavity is not actually invaded, and consequently hæmaturia and other evidence of a urinary disorder are frequently lacking.

The tumour spreads by direct invasion of adjacent structures to the peritoneum, omentum, and retroperitoneal tissues. Occasionally secondary deposits appear in the opposite kidney, in the lungs or other viscera.



FIG. 266. Adenocarcinoma (hypernephroma) of the kidney. $\times 450$. The tumour is composed of solid masses of large rounded cells, with small nuclei and very clear protoplasm. On the left is a thin-walled blood vessel.

(Laboratory of Royal College of Physicians of Edinburgh.)

The microscopic structure is that of a mixed tumour in which sarcomatous elements preponderate. The greater part of the tumour

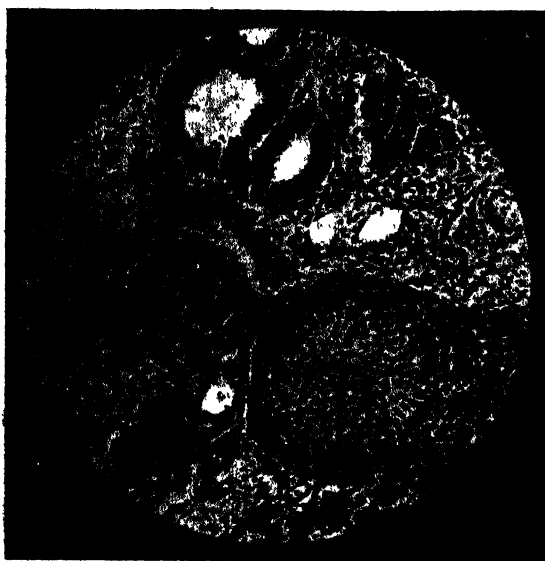


FIG. 267. Nephroblastoma. $\times 150$. Columnar-cell acini are set in a stroma of spindle cells.

(By courtesy of Prof. J. W. S. Blacklock.)

is made up of round or spindle-shaped cells, lying in a scanty delicate matrix, but in places there are gland-like collections of columnar or cubical cells, arranged in irregular acini, and occasionally there are islands of cartilage and of plain muscle fibres.

The origin of the tumour is not clear. It is generally accepted that the tumour is derived entirely from mesoderm, from some misplaced embryonic rudiment. Some authorities have ascribed it to vestiges of the mesonephros or of the metanephros, but

its structure suggests an even earlier origin. According to Wilms, it is derived from misplaced portions of a myotome, or primitive body segment, which normally gives rise to a whole excretory apparatus.

Other Tumours of the Kidney

Sarcoma of the kidney is extremely rare; it presents no special features differing from sarcoma elsewhere.

Simple tumours of the kidney are relatively common, though rarely of any clinical significance. Lipoma, fibroma and angioma have been described. Adenoma occurs, usually in adults and in small granular cirrhotic kidneys. Microscopically, it reproduces the structure of the renal tubules. It usually forms small, encapsuled, pale yellow tumours, but occasionally grows to considerable size.

TUMOURS OF THE RENAL PELVIS

Tumours of the renal pelvis are far less common than kidney tumours, and they differ from them in appearance, structure and behaviour. The renal pelvis, derived from a diverticulum of the Wolffian duct, is related more closely to the bladder than to the kidney; and in many respects its tumours resemble vesical tumours.

Two main varieties of tumour arise in the renal pelvis, angioma and epithelial tumour.

Angioma. Angioma is a benign tumour of rare occurrence, with the pathological features of angioma in other parts of the body (*see* p. 285). It arises most often in relation to one of the renal pyramids, and is of small size, rarely larger than a pea. It is of surgical importance on account of its tendency to ulcerate and cause hæmaturia.

Epithelial Tumours. Epithelial tumours are of greater importance. They arise from the transitional epithelium and have the characters of a papilloma or carcinoma. For convenience of description three forms are recognized: (1) papilloma, (2) papillary carcinoma, (3) epidermoid carcinoma. It should be understood, however, that, just as in the corresponding tumours of the bladder, there is no clear distinction between the different types, and intermediate forms may be recognized

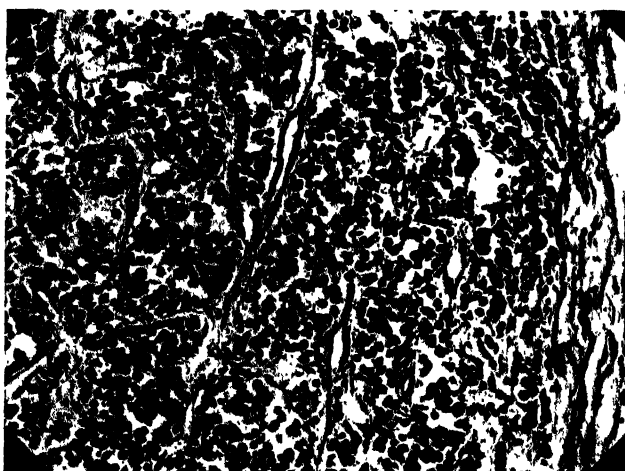


FIG. 268. Papillary carcinoma of the renal pelvis. The tumour is composed of rounded cells with hyperchromatic nuclei, supported on delicate strands of connective tissue. There is a definite papillomatous arrangement.

(Department of Surgery, University of Edinburgh.)

in continuous gradation between the simple papilloma and the malignant carcinoma. A tumour may be of simple appearance in one part, malignant in another. Moreover, a tumour of long duration and therefore presumably simple at first may later undergo malignant change. This change is most apt to develop in middle-aged or elderly subjects.

Papilloma. A papilloma is composed of delicate branching processes of connective tissue surmounted by transitional epithelium. It projects into the renal pelvis and tends to be pedunculated. When so situated as to cause partial obstruction of the ureter it gives rise to hydronephrosis. The tumour is very vascular and bleeds readily, leading to profuse and usually painless hæmaturia. A striking characteristic of the tumour is a tendency to disseminate to the ureter and even to the bladder, giving rise to daughter tumours similar in appearance to the parent growth. In such cases there is sometimes no demonstrable continuity between the primary and secondary tumours, and it is generally supposed that

the dissemination results from the implantation of tumour cells carried in the urine.

Papillary Carcinoma. A papillary carcinoma is more common than a simple papilloma in the renal pelvis. It is a bulky growth, which projects into the cavity of the renal pelvis and, in addition, infiltrates its wall. On the surface the growth may be covered with delicate vascular processes, but in the deeper part it is solid and sessile. The tumour infiltrates slowly and may invade the renal parenchyma. For a considerable time it may remain limited within the capsule of the



FIG. 269. Epidermoid cancer of the renal pelvis invading the kidney. Removed from a woman aged seventy-four years.

(Department of Surgery, University of Edinburgh.)

kidney and ureter, but eventually it tends to transgress this boundary and to involve the perirenal tissues. Ultimately, it may metastasize to the regional lymph glands and to the viscera.

A papillary carcinoma is very apt to obstruct the ureter and to give rise to hydronephrosis. The tumour may spread by implantation or by surface extension to any part of the hydronephrotic sac, so that finally the kidney may be represented by a thin shell of parenchyma enclosing a cavity occupied by the cauliflower-like growth. Infection by blood-borne organisms may occur.

Epidermoid Carcinoma. An epidermoid carcinoma is not entirely distinct from papillary carcinoma, and commonly a single specimen

presents combined features. As the title epidermoid indicates, it has many of the characters of a squamous-cell carcinoma (epithelioma). Typically, an epidermoid tumour tends to be flat, sessile and infiltrating, and it invades the perirenal tissues and metastasizes to lymph glands. Microscopically, the striking feature is the presence of squamous cells arranged in alveolar formation, somewhat as in skin carcinoma but lacking the cell nests so frequently found in that tumour. The occurrence of squamous cells in tumours derived from transitional epithelium is an interesting histological peculiarity, which is generally

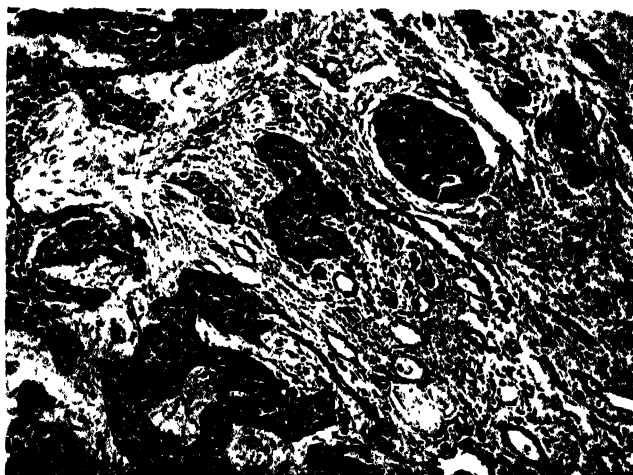


FIG. 270. Epidermoid cancer of the renal pelvis. Solid columns of malignant epithelial cells are invading the medulla of the kidney.

(Department of Surgery, University of Edinburgh.)

presumed to result from a pre-existing leukoplakia of the renal pelvis (*see* p. 620). In about 50 % of the cases arisen as a complication of renal calculus.

TUMOURS OF THE URETER

Primary tumours of the ureter are exceptionally rare. In general they resemble the epithelial tumours of the renal pelvis, and papilloma, papillary carcinoma and epidermoid carcinoma are recognized. They may be responsible for intermittent or persistent hæmaturia and may lead to hydronephrosis.

Secondary tumours of the ureter are more common. The ureter is invaded frequently by tumours of the cervix uteri, colon, bladder or prostate, or by metastatic growths in the retroperitoneal or pelvic lymph glands. Occasionally the ureter becomes the seat of secondary growths from tumours of the renal pelvis.

URINARY CALCULUS

This is an age-old disease, and its history goes back to the earliest periods of civilization. Urinary stones were known to the ancient

Egyptians, and have been found in mummies several thousand years old, and the operation of "cutting for stone" was practised several centuries before the Christian era. It would appear that at present the incidence of stone in the bladder is steadily decreasing, and in Britain this condition is much less prevalent now than during last century. The frequency of stone in the kidney and ureter, on the other hand, has shown an apparent increase, which is doubtless accounted for by improved methods of diagnosis.

Mode of Formation of Calculi. The urine contains a number of crystalline substances, which are held in heavily supersaturated solution through the protective action of colloids, such as mucin and chondroitin-sulphuric-acid. Under certain circumstances the crystalloids are precipitated, and if at the same time the colloids become modified, losing their solvent action and acquiring a kind of adhesive property, the precipitated crystals are bound together to form stones.

Thus it may be stated as a general principle that urinary stones are composed of crystalloid particles bound together by colloids. The two elements, crystalloid and colloid, are equally essential, for crystalloids alone, when precipitated, pass freely to the exterior, and for calculus-formation the adhesive properties of colloids are required.

The solution of both crystalloids and colloids is influenced to a large extent by the hydrogen-ion concentration of the urine. It seems likely that variations in this reaction play an important part in the formation of urinary calculi.

It is thus evident that the formation of calculi may result from an increase in the crystalloids excreted in the urine, from diminution, qualitative or quantitative, in the supporting colloids, or from an alteration in the hydrogen-ion concentration. Doubtless in many cases all these factors play a part.

Formerly it was thought that a diet rich in oxalates was responsible for the formation of oxalate stones, whilst one rich in purines was responsible for uric acid and urate stones. The present tendency, however, is against this view, for whilst undoubtedly a diet of oxalate-rich foodstuffs predisposes to the passage of oxalate crystals (oxaluria) it does not seem to lead to stone formation.

An increase in the blood calcium, with a consequent increased output of calcium in the urine, is one of the most important predisposing factors. In some cases a deficiency of phosphorus by altering the calcium-phosphorus ratio has a similar effect.

The increased blood calcium may be due to excessive intake of calcium or lack of phosphorus in the diet; probably the geographical incidence of urinary calculus is due in part to a local excess of calcium in the water and soil. Or the increased blood-calcium may be due to an increased absorption of calcium from the intestines, the diet being normal; such increased absorption may be influenced by excessive administration of vitamin D. Thirdly, the increased blood calcium may be a result of withdrawal of calcium from the skeleton. This is seen in its most severe form in osteitis fibrosa, in which as a result of parathyroid overaction the whole skeleton is decalcified. In this condition urinary calculus is a common complication. A similar withdrawal of

calcium from the skeleton is seen to a smaller extent in any chronic bone affection and even as a result of prolonged decubitus. Thus urinary calculus is a not uncommon complication in tuberculosis of bones and joints treated by prolonged recumbency. It may even follow fractures requiring prolonged treatment in bed.

The solvent properties of the colloids are also influenced by a number of factors, which are of significance in the ætiology of calculus. Any local lesion causing urinary stasis predisposes to calculi, which are thus common in the bladder behind an enlarged prostate or a urethral stricture, or in malformations such as horse-shoe kidney.

High concentration of the urine may be a factor, and is probably responsible for the frequency of calculi in such tropical regions as Northern Africa, Arabia, Persia, Mesopotamia and India.

Infection of the urine is a well-established factor in the ætiology of phosphatic stones. Urea-splitting organisms such as staphylococci are especially important in this respect. Infection by bilharzia (schistosomiasis) is one factor responsible for the frequency of calculi in Egypt.

Finally, the solvent properties of the colloids are greatly influenced by lack of vitamin A of animal origin. M'Carrison, whose observations have done much to throw light on the problem of calculus formation in India, has pointed out that the diet in that region is largely deficient in this essential vitamin. He has, moreover, produced urinary calculi in rats by feeding them on deficient diets, consisting of wholemeal flour, Indian millet or oatmeal. The stone formation in these experiments was assisted by adding calcium to the diet, but could be prevented by adding milk, butter or cod-liver oil. It seems likely that the prevalence of bladder stones in children in former days was due to a similar vitamin deficiency.

It is interesting to observe that in many cases of urinary calculus several of the above-mentioned factors may jointly be incriminated. Thus in "recumbency urinary calculi" such as are not uncommon in patients treated by recumbency during long periods for bone tuberculosis, fractures, etc., there may be evidence of generalized skeletal decalcification due to the immobilization and additional localized decalcification at the site of disease or injury, whilst in addition there is stagnation of the urine in the renal pelvis. In some cases also additional ætiological factors are to be found in high concentration of the urine caused by insolation and low fluid intake, hypovitaminosis D, and infection of the urine.

Types of Calculi

It is necessary to distinguish two principal varieties, primary and secondary stones. *Primary stones* are those that arise in an apparently healthy urinary tract and that are composed of substances present in the urine normally or as a result of metabolic disorders. Primary stones occur in acid urine. They require no preformed nuclei, but appear to arise from the slow precipitation of crystalloids in a colloid magma. Primary stones are usually composed of oxalates or of uric acid, rarely of cystin. *Secondary stones* are those that result from inflammation—

bacterial or aseptic—and their formation requires a preformed nucleus, which may be a primary stone, a foreign body, a clump of organisms, or a mass of inflammatory exudate. Since their development depends upon the liberation of ammonia from urea, they are found in alkaline urine. Secondary stones are almost invariably composed of ammonium-magnesium phosphate (triple phosphate).

Oxalate Calculi. Calcium oxalate is a normal constituent of the urine, approximately 15 to 20 mgm. being excreted daily in health. It is derived principally from the food, and after the ingestion of foods rich in oxalates it may be precipitated from the urine in crystalline form. Of the foods rich in oxalates the most common are rhubarb, spinach and asparagus; strawberries are of ill-repute in this respect, but without reason, for their oxalate content is less than that of potatoes. The absorption of oxalates from food depends to some extent upon the gastric acidity, and patients who suffer from hyperchlorhydria are especially prone to oxaluria.

Oxalate calculi are extremely hard. They may be smooth and rounded, or nodular like mulberries. Often they are of irregular shape and covered with sharp spicules. These physical characteristics modify the course and effects of oxalate calculi. The stones arise in the renal pelvis or calyces, and like other small stones similarly placed they are liable to be propelled down the ureter; but whereas stones of other composition usually pass rapidly into the bladder the rough-surfaced oxalate stones frequently become impacted in the ureter. In any position they irritate the mucous membrane and excite an outpouring of lymph and blood which renders them black or dark brown. The irritation is apt to lead to infection or to degenerative changes in the kidney, and the outpouring of lymph or inflammatory exudate favours secondary deposition of layers of phosphatic material.

Calculi of Uric Acid and Urates. Almost 1 mgm. of uric acid is excreted daily in the urine. It is partly of exogenous origin, from meat and other foods, and partly endogenous from the breaking down of tissues. In the lower animal kingdom and in birds and reptiles, uric acid forms the chief vehicle for excretion of nitrogen, but in higher animals and in man this function is assumed principally by urea.

Stones of uric acid and urates may arise in the renal pelvis or the bladder. They are hard but smooth, yellow or brown in colour, and usually rounded or oval. They may attain large size, and if situated in the renal pelvis may become moulded to the shape of that cavity. Stones are rarely composed of uric acid alone; commonly there is an admixture of urates, and not infrequently there are traces of calcium oxalate. Occasionally in children stones are composed chiefly of ammonium urate; they are yellow, soft and friable.

Cystin Calculi. Cystin calculi, though uncommon, are of especial interest from their close relationship to a metabolic disorder. Cystin is an amino-acid with a high sulphur content; in normal subjects the sulphur is oxidized completely and is excreted as sulphates, but in a small proportion of persons some "inborn error of metabolism" causes the cystin to appear in the urine unchanged. In the urine it is deposited

as flat, colourless, hexagonal crystals, easily recognized on microscopic examination. After the urine has stood for some time the sulphur may become combined as hydrogen sulphide, and this is recognizable by its smell.

Cystinuria is usually a familial disorder, and may be present throughout life. Only a small proportion, about 2%, of the subjects of cystinuria develop stones, but in this small minority the tendency to stone formation is very great. The stones often appear in childhood and are multiple, and after their removal by operation others tend to form. They are moderately hard, with smooth surface, and of yellow, waxy appearance. On exposure to light and air they gradually darken to an olive-green colour. Cystin stones usually form in the renal pelvis and calyces, and when small they readily pass down the ureter to the bladder.

Phosphatic Calculi. Normal urine contains phosphates derived from the breaking down of tissues rich in phosphorus and, to a less extent, from absorption in food; but phosphatic stones are not composed of these substances but of triple phosphate (ammonium-magnesium phosphate), of which only a trace is normally present. The conversion of the phosphates present in health into triple phosphates depends upon the liberation of ammonium carbonate from urea, and as this process is often due to the decomposition of urea by micro-organisms it follows that phosphatic stones are frequently the result of a urinary infection.

Phosphatic stones are grey or of a dirty white colour and may be moderately hard or soft and friable; they are always deposited around some preformed nucleus, such as primary oxalate or urate stone or a foreign body; often they attain large size and they form the majority of "stag-horn" and other large irregular calculi in the kidneys, ureter or bladder. Moreover, since they often arise from staphylococcal or streptococcal infections that resist treatment, recurrence after operation is common. The second kidney also may become affected.

Rare Constituents of Stones. *Xanthin*, like cystin, is a product of abnormal metabolism, but stones containing more than a trace of xanthin are excessively rare. *Calcium carbonate* often takes part in the formation of phosphatic calculi and may rarely be the predominant constituent of a stone. *Indigo*, derived from indol, is occasionally found, and if present in quantity it may impart its colour to the stone. So-called *fibrin stones*, small putty-like masses found in grossly infected kidneys, arise from the inspissation of old blood clot or an inflammatory exudate. Rarely *bacteria* form the principal constituents of small soft concretions.

Stones in the Kidney

The majority of urinary stones are formed in the kidney. They are usually single, less commonly multiple, and are formed in the calyces or in the renal pelvis, never in the parenchyma. Usually they lie in the lower major calyx and may remain there through life or they

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may travel to the ureter and the bladder. The stones may retain their purity, but often, from irritation and inflammatory change, they become coated with phosphates. At first a renal calculus is rounded or oval, but in its growth it may become moulded to the shape of a calyx or a portion of the renal pelvis; phosphatic stones often form a complete cast of the pelvis and calyces—the so-called stag-horn stone.

Any renal calculus, but especially one associated with obstruction to the flow of urine, may lead to gross pathological changes in the kidney—interstitial fibrosis, hydronephrosis, pyelonephritis and pyonephrosis. Of infective complications those from staphylococci and streptococci are the most dangerous, for these are urea-splitting organisms which render the urine alkaline and lead to extensive phosphatic precipitation. Not infrequently also the organisms tend to infect the other kidney and to produce similar changes there.

Stones in the Ureter

Stones in the ureter always originate as renal stones which have been arrested during descent, and they are usually oxalate stones which, from their irregular shape, are particularly liable to become impacted. Impaction usually occurs at one of the sites of normal narrowing, near the entrance to the bladder, at the crossing of the iliac vessels, or at the pelvi-ureteral junction (in that order of frequency). When impacted, a stone ulcerates the mucosa, so that it may lead to subsequent fibrosis. Sometimes the ulcer deepens so that the stone comes to lie in a pocket in the periureteral tissues, and no longer obstructs the flow of urine. At first a ureteral stone maintains its original shape and composition, but it rapidly becomes encrusted with phosphates, and it then becomes elongated, conforming to the shape of the ureter.

Sometimes the ureter is completely obstructed, but usually a certain amount of urine can reach the bladder; in either case the ureter above dilates and hydronephrosis develops. If the obstruction is not soon relieved the renal parenchyma becomes thinned out, fibrous and functionless. Experimentally, it is found that the kidney will not recover after a complete obstruction of longer than two or three weeks; particularly is this so if the other kidney is able to compensate for the loss; but if the second kidney is diseased, the first may recover to some extent (renal counterbalance).

If a stone lies in the ureter without causing much obstruction there may sometimes be an increased flow of urine from that side, possibly from reflex stimulation or more probably from chronic interstitial change in the kidney. A ureteral stone causes colicky pains during its descent, and dull pains in the loin from over-distension of the renal pelvis; it may give rise also to local pain in the lower quadrant of the abdomen, and on the right side this, with reflex boarding of the muscles, may simulate appendicitis. Frequency of micturition may be present, from irritation of the ureter and consequent reflex stimulation.

Stones in the Bladder

Stones may originate in the bladder or they may reach it from the kidney. As in the kidney, stones originating in the bladder may be

of primary or secondary type. Primary stones may form in a perfectly healthy bladder, but are rather more common where there is some obstruction to the passage of urine, from prostatic enlargement or other cause. Secondary stones are much more common, especially when cystitis is present. They are composed principally of triple phosphates, deposited upon a nucleus such as a primary stone, or a mass of inflammatory exudate. In rare instances the nucleus is formed by objects introduced along the urethra, and hairpins, lead pencils or even portions of catheters have been responsible. Similarly ligatures of catgut or silk may originate stone formation.

Not infrequently large stones resulting from secondary deposition on a primary calculus are laminated, and layers principally composed of phosphates alternate with those of other substances. A classical example was the stone of Napoleon III., which consisted of laminæ of uric acid alternating with phosphates. At that time all stones were thought to arise from disordered metabolism, and the alternation of laminæ was believed to follow changes in the amount of purin bodies or of phosphates consumed at different times; the layers of uric acid were



FIG. 271. Multiple renal calculi composed of uric acid and urates. A calculus of similar composition impacted at the pelvi-ureteral junction had led to hydronephrosis.

(Department of Surgery, University of Edinburgh.)

attributed to the ample dietary of the Paris season, and the phosphatic deposits to the waters of Vichy consumed during the annual "cure." A more probable explanation, however, though less picturesque, is that the phosphatic laminæ were attributable to recurring exacerbations of cystitis.

Stones in the Urethra

Stones in the urethra are usually migratory stones that have passed from the kidney or bladder; they lodge in the urethra near one of the sites of normal narrowing, either in the prostatic urethra or

close to the external meatus; when impacted they become coated with phosphates and assume an elongated shape. Occasionally stones originate in the urethra, but only in the presence of a stricture and infection. They obstruct the flow of urine and lead to bilateral

hydronephrosis, often with infection. Sometimes the stone ulcerates through the urethral mucosa and comes to lie in a shallow diverticulum, and it may lead to extravasation of urine and to a fistula. Occasionally a stone impacted in the female urethra may ulcerate into the vagina, and may remain there for many years. Such a stone (the so-called vaginal stone) may attain considerable size from the accretion of phosphates, and may assume an elongated shape. A radiogram may demonstrate a central laminated portion, the source of the stone.



FIG. 272. Multiple renal calculi composed of uric acid and urates. The stones lie in the renal pelvis and the lower calyces, and have given rise to an extreme degree of hydronephrosis of the intra-renal type. Note that some of the stones are faceted by mutual pressure.

(Department of Surgery, University of Edinburgh.)

ANURIA

Anuria—the arrest of secretion of urine—may occur in many different circumstances, and, according to the nature of the conditions causing it, three types are recognized: (1) pre-renal, (2) renal, and (3) post-renal.

(1) *Pre-renal anuria* is usually due to circulatory changes that interfere with filtration of fluids from the blood as it passes through the glomeruli. The blood pressure in the glomerular vessels is normally about 90 mm. of mercury, and if the general arterial pressure falls far

below this level renal secretion ceases. Pre-renal anuria arises in any state associated with sustained reduction of blood pressure, for example, in severe shock, or in anhydræmia from excessive loss of fluids by the skin or bowel. It may occur after spinal anæsthesia, and in this case the anuria is transient and passes off when the blood pressure is restored to normal.

(2) *Renal anuria* is due to destructive changes in the secretory epithelium of the kidney. It occurs in most typical form in acute nephritis, in poisoning by phosphorus or by corrosive sublimate, which cause necrosis of the kidney, or in eclampsia and acute yellow atrophy of the liver.

A somewhat similar form of anuria may occur from the precipitation

of sulphonamide drugs if the urine is unduly concentrated ; it is deposited in crystalline form in the renal tubules or the ureters.

Anuria of renal origin may also be associated with acute bacterial infections of the kidneys and, in such cases, pre-existing disease of the kidneys predisposes to its occurrence. Anuria may also occur reflexly after sudden evacuation of urine from a distended bladder in subjects of chronic enlargement of the prostate. In such cases the anuria is believed to be due to sudden engorgement of the vessels of the kidney. In rare instances anuria may follow upon blood transfusion and is then due to precipitation of hæmatin from hæmoglobin in the renal tubules. Usually the urine has been of high acidity and salt concentration. Overheating of the transfused blood would seem to be an important exciting factor.

(8) *Post-renal or obstructive anuria* is the most important variety from the surgical standpoint. The obstruction may be due to calculi, new growths, accidental ligation of the ureter, or inflammatory swelling of the mucous membrane of the renal pelvis or of the ureter. For its development the obstruction must be bilateral or, as is commonly the case, must involve the only functioning kidney. It is thought that in some instances when one kidney is obstructed the opposite kidney ceases to secrete through reflex nervous inhibition (reno-renal reflex).

Calculous anuria may occur under many different circumstances which are often determined by the antecedent condition of the kidneys and the ureters. Swift Joly recognizes four main types : (1) obstruction of both kidneys or of both ureters ; (2) obstruction of the only functioning kidney ; (3) obstruction of one kidney, its fellow being diseased ; and (4) obstruction of one kidney, its fellow being apparently healthy. Clinically, the first and second types are sometimes indistinguishable.

Simultaneous bilateral obstruction of the kidneys or the ureters is usually due to calculi. The calculi are often small and are generally impacted in the upper part of the ureter. The presence of a large calculus in one kidney and of a small one in the opposite ureter, is usually an indication that the small stone has recently migrated and obstructed the ureter.

Obstruction of the only functioning kidney may occur in either of two sets of circumstances : (1) with a congenital absence of one kidney ; (2) when one kidney has been previously removed, or has been destroyed by diseases such as tuberculosis, or pyonephrosis. Obstruction of one kidney with contralateral disease is one of the commonest types of calculous anuria. The unobstructed kidney is usually the seat either of infection or of chronic interstitial nephritis.

Obstruction of one kidney, its fellow being apparently healthy, rarely gives rise to complete anuria. The anuria is usually temporary and is believed to be due to reflex suppression of urine on the healthy side. It is generally believed that fatal anuria follows unilateral obstruction only when the other kidney is diseased.

In calculous anuria when the kidney is exposed at operation it is found to be enlarged, congested and plum-coloured, and the surrounding

tissues are cedematous. The renal pelvis may be distended with urine, but sometimes it is almost empty.

EXTROVERSION OF THE BLADDER (*Ectopia Vesicæ*)

In this congenital malformation there is a defect in the lower part of the anterior abdominal wall and in the anterior wall of the bladder, and through the defect the posterior wall of the bladder appears at the surface. The condition is believed to arise from failure of the forward growth of the anterior part of the cloacal membrane.

The defect is oval or rounded and lies in the mid-line below the umbilicus. The posterior bladder wall is projected forwards by the pressure of the viscera behind and forms a bulging swelling of deep-red colour, separated peripherally from the skin of the abdominal wall by a ring of fibrous tissue. Usually the umbilicus is displaced downwards and it may be involved in the scar tissue and obscured by encrustations.

The ureters ascend from the pelvic floor and open at the surface near the lower rim of the protrusion, and jets of urine may be observed to issue at intervals. The constant leakage of urine at the surface forms the most distressing feature of the condition. Often from infection or from the irritation of clothes or dressings the exposed bladder surface becomes inflamed and it may be raised in cedematous folds and ulcerated. Carcinoma occasionally supervenes; it is usually an adenocarcinoma arising in mucous membrane, the seat of cystitis cystica.

Exstrophy of the bladder is generally associated with other maldevelopments of the parietes and the lower urinary tract. Usually the symphysis pubis is absent, and the pubic bones, which may be several centimetres apart, are united by a thick fibrous band. The wide separation of the pubes sometimes leads to a waddling gait like that associated with congenital dislocation of the hips.

The exstrophy is accompanied by epispadias, and in the male, the sex commonly affected, the penis is drawn up and fixed to the abdominal wall. Often the testes are ectopic and the scrotum may be ill-developed. The prostate and vesicles may be absent or atrophic. In the female there may be maldevelopments of the uterus and vagina.

CONGENITAL OBSTRUCTION AT THE VESICAL OUTLET

(*Congenital Vesical Sphincteric Stenosis*)

In this condition, which is confined to boys, there is from birth difficulty in emptying the bladder. There is difficulty in starting the act of micturition and the stream lacks force and volume, and frequency of micturition and dribbling are usually present.

In the early stages the bladder is small and thick-walled from hypertrophy of its muscular coat, but at a later stage it becomes dilated so as to form an obvious swelling in the abdomen. The neck of the bladder and the upper part of the prostatic urethra are dilated to form a funnel-like prolongation from the base of the bladder, and in many

instances a fold of mucous membrane projects into the lumen of the urethra from the region of the verumontanum, or less commonly from the anterior margin of the neck of the bladder.

It is characteristic of this form of urinary obstruction that no difficulty is usually experienced in passing an instrument into the bladder.

If the disease is not treated the ureters dilate and hydronephrosis develops. The ureters may be so greatly dilated as to be felt through the abdominal wall. The ureteral dilatation depends upon a loss of normal valvular action at the uretero-vesical orifice, and this can be readily demonstrated in radiograms after filling the bladder with an opaque fluid, when it is noted that the fluid regurgitates into the ureters, which appear as tortuous channels with a lumen that may be as great as that of the small intestine. Death usually occurs before the age of ten years from uræmia, often accelerated by extension of infection from the bladder.

The aetiology of this form of urinary obstruction is not finally settled. Hugh Young attributed the obstruction to the valve-like action of folds of mucous membrane in the prostatic urethra, and he claims to be able to demonstrate such folds by cystoscopic examination. In his experience destruction of the folds is sufficient to relieve the obstruction. Other observers have not been able to demonstrate obstructing valvular folds with such constancy. Certainly at post-mortem examination in a number of cases no mechanical obstruction has been found, and their absence has led to the belief that the obstruction is, in some cases at least, of a functional character and due to an inherent defect of the neuro-muscular mechanism concerned in micturition.

DISEASES OF THE URACHUS

The urachus, or allantoic canal, develops with the bladder from the ventral part of the cloaca and is about 5 to 6 cm. in length. In embryonic life it forms a patent channel extending from the apex of the bladder into the umbilical canal. In later life it is united with the obliterated umbilical arteries to form the ligamentum commune which extends to the umbilicus. Below it passes into the muscular coats of the bladder. Normally the urachus has a fine lumen which, in about 30 per cent. of subjects, is continuous for a short distance with that of the bladder.

Developmental Abnormalities. These are extremely rare and unimportant. In some instances the urachus does not develop, and then the apex of the bladder is found at the umbilicus, where it may form an external fistula. Varying degrees of non-descent of the bladder and consequent imperfect development of the urachus may occur, and they may be associated with retarded closure of the bladder and with external fistulae.

Cysts and Tumours of the Urachus. Small sacculations may occur in the lower part of the urachus; they are due to distension by secretion of the normal epithelium-lined spaces. In some instances a urachal cyst

is due to degeneration of a small adenoma of the epithelium of the urachus.

Simple tumours, such as adenoma, fibro-adenoma and fibro-myxoma have been described but they are exceptionally rare. A sarcoma may arise from the fibrous investments of the urachus, but it also is rare.

A *carcinoma* may arise from the epithelial remains. It takes origin at the apex of the bladder, which may be invaded by it, but it tends to spread widely in the extraperitoneal tissues before the bladder is extensively involved. A carcinoma of urachal origin is usually of columnar-cell type, and often shows colloid degeneration.

DIVERTICULA OF THE BLADDER

A diverticulum of the bladder may be congenital, but the majority develop in adult life, especially in men over fifty years. They may be single or multiple; and they may be of small size or larger than the bladder itself. Diverticula should be distinguished from the shallow pouches found between the trabeculae of a hypertrophied bladder, from the prolongations of part of the bladder into inguinal or femoral herniae, and from septic paravesical cavities communicating with the bladder.

Ætiology. Diverticula in infants and young subjects are very rare, are usually congenital, and associated with a contracted urethral orifice or valves. In the majority of cases diverticula are acquired in adult life as a result of urethral obstruction, and the extreme rarity of diverticula in women is probably accounted for by the infrequency with which they suffer from interference with the outflow of urine.

Chronic enlargement of the prostate and stricture of the urethra are the two diseases most often responsible for diverticula, and as diverticula are only present in a limited number of cases, it appears that there must be an inherent weakness of the walls of the bladder in some subjects. The prostatic enlargement is seldom more than slight.

Diverticula usually arise just above and lateral to a ureteric orifice at the junction of the trigone with the rest of the bladder, and this rather constant site of origin suggests that in these positions the walls of the bladder are less resistant to pressure than elsewhere.

In rare instances a diverticulum may result from traction caused by adhesion of the bladder to neighbouring organs, and in such cases there may be a history of previous pelvic cellulitis.

Morbid Anatomy. Diverticula may be present at any part of the bladder, but they are found most frequently on the lateral walls in the neighbourhood of the ureteral orifice. Less often they are found at the posterior surface of the bladder immediately above the interureteric bar. In many cases the diverticula are placed symmetrically. When they are multiple, one of them is often large, the others small.

The orifice of the diverticulum is usually small, with sharply defined margins, giving it a punched-out appearance when viewed at cystoscopy. An oval or slit-like orifice is sometimes found, but it is less common. The ureter may open on the margin of the orifice of the diverticulum, or it may be directed into the interior of the sac.

The mucous membrane around the orifice is often puckered in a radiate fashion. Trabeculation of the bladder confined to the region of the orifice is often noted, and the interureteric bar may be hypertrophied on the side of the diverticulum.

The diverticulum varies in thickness, and all the coats of the bladder are represented in it. The mucous membrane and the submucosa are thin. Muscle fibres are most abundant at the neck of the diverticulum, and if the sac is large they may be very attenuated or absent towards its fundus. Its abdominal surface is covered by the perivesical fascia, and there is often a considerable deposition of fat around it. From infection, the diverticulum may become very firmly adherent to the pelvic viscera.

Pathological Effects and Complications of Diverticula. By pressure or by traction, a diverticulum may cause constriction of the lower end of the ureter, and subsequent dilatation of the kidney, and if infection is present in the bladder, ascending pyelonephritis may supervene.

A large diverticulum has no power of muscular contraction, and depends mainly on gravity for expulsion of its contents. Stagnation of the urine within it predisposes to infection, and therefore cystitis is one of the commonest complications. From the diverticulum stagnant purulent urine may escape from time to time. As a result of infection, multiple phosphatic calculi frequently develop in the interior of a diverticulum. Perforation of an infected diverticulum is a rare complication.

A carcinoma may develop at the orifice of a diverticulum or in its interior.

CYSTITIS

The bladder is remarkably resistant to infection by pyogenic organisms, and may remain healthy even though the urine be heavily infected. This is especially true if the bladder is normal in other respects, and cystitis is almost always dependent upon some predisposing factor which favours the lodgment or growth of micro-organisms in the bladder.

The most important predisposing factor is obstruction to the outflow of urine which leads to imperfect emptying of the bladder. For this reason Cystitis is common in association with prostatic enlargement or with urethral stricture, and it is an almost inevitable complication of lesions of the brain and spinal cord associated with retention of urine. Cystitis is very apt to develop, also, as a result of urinary stasis in a diverticulum of the bladder, or, in females, as a complication of cystocele.

A second predisposing factor of some importance is the presence of a foreign body in the bladder. A stone, for example, frequently determines the onset of cystitis, or it may aggravate any existing infection. Foreign bodies introduced along the urethra, for example lead pencils, portions of rubber catheters, etc., may give rise to especially severe types of cystitis, and even small foreign bodies such as surgical sutures inserted into the bladder wall may aggravate an infection.

Tumours of the bladder also predispose to cystitis, probably because they afford an ulcerated surface and an abundance of necrotic material. Malignant tumours are almost invariably accompanied by cystitis, and simple tumours are very apt to become infected after fulguration, when a part or the whole of the tumour is necrotic.

The Organisms. The organisms of cystitis are varied. Coliform bacilli are undoubtedly the most common, especially in the milder forms of chronic cystitis. Staphylococci and streptococci are often present, either alone or with *bacillus coli*. They are especially common in purulent cystitis associated with obstruction to the outflow of urine, and since they render the urine alkaline they are important factors in the production of phosphatic incrustations or stones. Less often, *bacillus proteus*, *bacillus typhosus*, and other organisms are found.

Avenues of Infection. The avenues of infection in cystitis are not always obvious, and no doubt they vary in different cases. Often it seems likely that cystitis is secondary to an infection of the kidney; for example, pyelitis or pyelonephritis, although it is remarkable, as has already been noted, that in many cases the bladder may withstand such an infection during a long period.

In other cases the bladder is infected by way of the urethra. This is probably the commonest mode of infection, and it seems likely that the comparative frequency of cystitis in the female is due to the shortness of the urethra. In some cases, especially in males, the infection is introduced by a catheter. In normal circumstances the urethra contains few or no organisms, and instrumentation is comparatively free from risk, but when the urethra is diseased or is the seat of stricture even the most scrupulous care will not always prevent the onset of cystitis, especially if the urine is subsequently allowed to stagnate in the bladder.

Pathological Changes. It is customary to describe two varieties, acute and chronic cystitis, and either may vary considerably in the degree of its pathological changes.

In *acute cystitis* the inflammation affects the whole extent of the mucous membrane, but is especially obvious at the trigone and base of the bladder. The mucous membrane, normally of pale yellowish colour, becomes intensely hyperæmic and of bright red colour. The blood vessels, normally visible as delicate branching filaments, become dilated and tortuous, and there may be petechial hæmorrhages. Flakes of exudate float in the urine and adhere to the inflamed bladder wall.

In some cases of catarrhal cystitis these are the only pathological changes, but often, in addition, the mucous membrane is greatly œdematous and in places eroded, so that the urine contains blood as well as pus and organisms. Rarely, extensive areas of mucous membrane may desquamate.

In *chronic cystitis* the pathological changes vary greatly. They are always most obvious at the base and neck of the bladder, and it is important to observe that in contrast to tuberculous cystitis the regions of the ureteral orifices are not particularly affected, though they may share in the general inflammatory changes.

In the mildest forms of chronic cystitis there may be little change visible except a slight increase in the vascularity of the bladder base, or

the bladder wall may appear paler than usual and of yellowish white colour. In other cases the mucous membrane is œdematous, thickened, and with a rough, velvety or granular appearance. Sometimes the œdema is considerable, and the mucous membrane is then swollen and projects in smooth, rounded bullæ which may even resemble simple polypoidal tumours. In more severe degrees of cystitis the mucous membrane is ulcerated, and covered with adherent flakes of pus. Ulcerative cystitis is often due to ammonia-forming organisms which render the urine alkaline, and often it is associated with the deposition of calcium phosphate, either as incrustations of the ulcerated wall or as calculi.

Rare Forms of Cystitis

Alkaline Incrusted Cystitis. This form of cystitis is due to the implantation of *B. proteus* in a bladder already the seat of inflammation. It is a very chronic and intractable form of cystitis. The disease occurs most often after childbirth, when injury to the bladder has necessitated catheterization. It may follow operations for enlargement of the prostate, or for urethral stricture.

The bladder is generally reduced in size and bleeds readily on examination. The mucous membrane is œdematous, and adherent to it are flat circumscribed plaques of gritty, phosphatic material. The incrustations are usually confined to the trigone and neck of the bladder, but sometimes the whole of the mucous membrane may be affected. When the incrustations are detached with an instrument a bleeding surface composed of granulation tissue is exposed. The urine is alkaline in reaction and contains blood, mucus and leucocytes. Sometimes gritty material is passed in the urine.

Cystitis Emphysematosa. This form of cystitis, which may occur in either sex, is characterized by the presence of multiple small gas-containing cysts in the subepithelial tissues of the bladder. The cysts, which are rarely larger than a large pin's head, project towards the interior of the bladder. The whole surface of the bladder may be affected or the lesion may be confined to one zone. The urine may be normal, but is usually infected.

Cystitis Cystica. In this somewhat rare condition, which is found in association with infections of the urinary tract, the mucous membrane of the bladder is the seat of numerous small cysts which microscopically have an adenomatous appearance. The lesion may be confined to the bladder, but very occasionally a similar condition is present in the ureters and the renal pelvis.

The cause of the cyst formation is not certain. Virchow suggested the cysts were due to blocking of crypts of glands in the mucous membrane. More recently it is suggested that cellular degeneration in inflamed and œdematous mucous membrane is responsible. Appearances similar to cystitis cystica have been produced experimentally in rabbits by injuring the mucous membrane of the bladder by curettage.

The cyst formation is usually confined to the trigone and the region of the ureteral orifices. One or more of the cysts may become peduncu-

lated. When several are clustered together they have the appearance of bullous cedema.

Localized Interstitial Cystitis (Hunner's Ulcer). In this form of chronic cystitis the bladder is the seat of one or more small linear or circular ulcers, which are most often present at the junction of the trigone and lateral walls. The ulcers are clear cut and have a red base which may bear fibrin on its surface, but sloughing such as is present in tuberculous ulcers never occurs. Neither pus cells nor organisms are present in the urine. Small engorged vessels radiate from the ulcers. At the site of ulceration the walls of the bladder are slightly indurated and thickened, due chiefly to cedema and to a less extent to fibrous tissue proliferation and round-cell infiltration. Occasionally the fibrosis may extend to the paravesical tissues, or even to the peritoneum, to which the bladder may become adherent.

As a result of the ulceration and fibrosis, the capacity of the bladder is reduced, often to 150 c.cms., and when the bladder is distended to this point and the ulcerated surface becomes stretched there is severe pain with urgency of micturition, which are at once relieved when the bladder is emptied.

At cystoscopy the ulcers appear as mahogany coloured areas. When the bladder is distended blanching occurs, and cracks appear on their surface. The mucous membrane is fixed to the sub-mucosa around the site of ulceration, and the ulcer bleeds easily if touched.

Nothing definite is known of the ætiology of this condition, but it has been presumed that it is due to infection of the wall of the bladder from a distant focus.

Leukoplakia of the Bladder. In this condition the transitional mucous membrane of the bladder undergoes metaplasia and assumes the characteristic features of a squamous-cell membrane. A similar change has been observed in the mucous membranes of the renal pelvis and of the gall-bladder. In the bladder leukoplakia is invariably accompanied by the signs of chronic cystitis, and it is to be regarded as a hyperplastic reaction of the tissues to the irritation induced by chronic inflammation. Its main pathological significance is that it is possibly to be regarded as a precancerous condition.

TUMOURS OF THE BLADDER

The bladder, especially in the male, is a fairly common site for tumours. They are generally of an epithelial nature, although various types of connective tissue tumour such as fibroma, myoma and angioma have been described.

The majority of bladder tumours take origin in a previously healthy mucous surface, but occasionally there are definite precancerous factors. It is well known that aniline dye workers are specially prone to the formation of papilloma, and this is attributed to irritation of the mucous membrane of the bladder by long-continued excretion of the dyes. Schistosomiasis in Egypt frequently predisposes to papilloma and carcinoma. Leukoplakia of the bladder, usually associated with chronic cystitis, may also be the starting point of a new growth: but.

generally, cystitis cannot be regarded as a definite or common precancerous condition.

PAPILLOMA

(Villous Papilloma)

A papilloma of the bladder may be sessile, but is usually pedunculated. It is much commoner in men than in women, and often it arises in early adult life. It may be single or multiple, and varies greatly in size, sometimes attaining the dimensions of a golf ball. It shows a special predilection for the base of the bladder, and is specially prone to arise above or lateral to the ureteral orifice.

In its usual form the tumour is pedunculated, and consists of

a central stem surrounded by delicate branching filaments or villi, which give an appearance often likened to a sea anemone. In other cases there is no central stem and the villi take origin directly from the mucous membrane of the bladder. Sometimes the tumour is somewhat sessile and lobulated, resembling a raspberry.

Microscopically, the central core is composed of fibrous tissue which is prolonged in delicate strands into the villi of the tumour. Occasionally the stroma contains plain muscle fibres and elastic tissue. The



FIG. 273. Villous papilloma of the bladder. $\times 110$. Two villi are seen, consisting of transitional epithelium mounted on delicate cores of connective tissue. Note the numerous large capillary blood vessels.

(Laboratory of Royal College of Physicians of Edinburgh.)

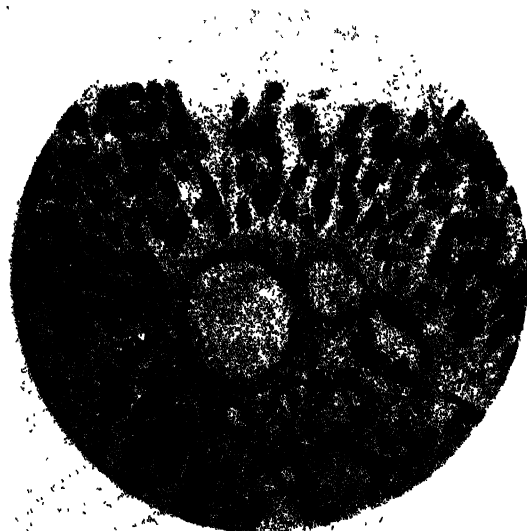


FIG. 274. Villous papilloma of the bladder. $\times 275$. From the same section as Fig. 273. Note the elongated type of transitional epithelial cells and the large capillary blood vessels.

(Laboratory of Royal College of Physicians of Edinburgh.)

epithelium, which covers the fibrous core and each of the villi, resembles that of the bladder, and is of transitional character. It is composed of cylindrical cells, arranged regularly in a radiate fashion. The stroma contains numerous large, thin-walled capillary vessels. The great vascularity of the tumour is very apt to cause hæmaturia, which is often profuse and generally painless. A pedunculated papilloma may become engaged in the urethra, and thus cause strangury or retention of urine. Portions of the tumour may be passed in the urine.

At its inception a papilloma is generally a benign growth, but is very prone to malignant change, especially in elderly persons. Malignant change is evidenced by a more sessile form of growth, and by a tendency



FIG. 275. Papillary carcinoma of the bladder.

(Museum of Royal College of Surgeons of Edinburgh.)

to involve the vesical mucosa around the pedicle. In some cases the mucosa for a considerable distance around becomes congested and of granular appearance as a result of early neoplastic changes in it. Vesical papilloma is often associated with a tendency to recurrence after operation. The "seedling" tumours may reproduce the structure of the parent growth, or they may assume malignant characters. They may be large and pedunculated, but more often are small, multiple and sessile. This form of metastasis is usually attributed to implantation of free cells from the tumour on to the healthy mucous membrane.

CARCINOMA

Carcinoma of the bladder may originate in a villous papilloma, or it may arise *de novo* in a bladder that has appeared healthy. Usually it

is situated at the base of the bladder, and it rarely originates at the fundus. Two principal varieties of carcinoma are recognized, the papillary and the infiltrating, but the appearance and microscopic features vary both in different tumours and in different parts of the same tumour, and between the two principal varieties there are intermediate forms which render exact classification difficult. A third variety, an adenocarcinoma, is rare.

The papillary carcinoma generally arises in a villous papilloma. When a simple papilloma undergoes malignant change it grows more rapidly and forms a bulky, soft mass which may eventually fill the greater part of the bladder. Microscopically, the papillary formation of the growth persists, but the uniformity of structure so characteristic of the simple papilloma is lost. The epithelial cells are arranged irregularly, and in places are heaped in solid masses. The cells vary in size and shape, their nuclei are hyperchromatic, and mitotic figures are present.

Through impairment of blood supply, the central and superficial portions of the tumour are liable to necrosis and ulceration. The ulcerated surface bleeds readily, and sometimes profusely, and the blood may be so copious as to clot in the bladder. The presence of necrotic tissue predisposes to infection, and cystitis is very likely to develop.

In addition to enlarging superficially, the tumour tends to spread deeply and to infiltrate the bladder wall. The mucous membrane around the tumour becomes thickened and nodular and subsequently ulcerates. Later fresh tumours may appear in other parts of the bladder. They are especially liable to recur after operative removal of the principal mass.

The infiltrating carcinoma, the so-called epidermoid cancer, may develop in one part of a papillary growth or it may arise primarily. It is generally a scirrhous growth which does not project far into the cavity but spreads widely in the bladder wall. It forms a shallow ulcer surrounded by a raised, indurated margin. On microscopic examination the growth is composed principally of solid masses of epithelial cells supported in a fibrous stroma. Generally in some parts of the tumour there is evidence of papillary formation. Sometimes the appearance suggests a squamous-cell carcinoma, and there may even be cell nests. Tumours presenting this feature are generally presumed to have arisen in mucous membrane that has assumed a squamous-cell type following leukoplakia. Usually they are accompanied by purulent cystitis, and the malignant ulcer may be partly obscured by phosphatic deposits and pus.

Adenocarcinoma of the bladder is rare and is believed to arise in the small tubular glands occasionally found in the mucous membrane at the trigone of the bladder or in an area of cystitis cystica. Tumours of this type tend to project into the cavity of the bladder and to form soft bulky growths, which are very liable to myxomatous change and to necrosis and occasionally distant metastasis.

Spread of Vesical Carcinoma. Carcinoma of the bladder grows slowly, and spreads principally by direct infiltration of adjacent tissues. At first, and for a considerable time, it remains limited to the bladder wall, and at this stage complete extirpation would be possible but for

the technical difficulties of the operation and the dangers consequent on diversion of the urinary outflow. Later the tumour infiltrates the soft tissues of the pelvis, and at this stage it is very apt to involve one or both ureters and to cause obstructive anuria; or it may perforate the vagina or the rectum and lead to a urinary fistula. Eventually the tumour may spread to the regional lymph glands. Rarely it metastasizes to distant sites, especially to the vertebræ and pelvic bones and to the lungs.

SARCOMA OF THE BLADDER

Sarcoma of the bladder is a rare tumour which may arise in childhood or in adult life. It originates in the submucous coat of the bladder and grows to large size, forming a soft mass which is very liable to hæmorrhage and necrosis. The tumour projects into and may almost fill the bladder, and it spreads also in the connective tissue planes of the pelvis and exerts pressure upon the bladder, the urethra or the rectum. On microscopic examination it consists principally of spindle-shaped cells. Often in certain parts of the tumour there is evidence of abortive attempts at glandular formation, and there may be areas of myxomatous tissue and even striped muscle fibres. In such cases the growth may be regarded as a mixed tumour or rhabdomyosarcoma.

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CHAPTER XXXII

DISEASES OF THE MALE GENERATIVE ORGANS

Development of the Genital Tract. The genital gland (testicle or ovary) first appears as an elongated mass on the medial aspect of the mesonephros or Wolffian body (*see* p. 607), where it forms a subsidiary ridge projecting forwards into the body cavity. Lateral to it there appears the Müllerian duct, and both the Müllerian duct and the Wolffian duct partake in the evolution of the genital tract, the Müllerian duct in the female and the Wolffian duct in the male.

At about the seventh week of intra-uterine life the genital tract passes through a complex metamorphosis, for at this time the genital gland descends from its primitive position in the lumbar region towards the groin and scrotum, or towards the true pelvis, and with the gland migrate also the upper (cephalad) portions of the Wolffian and Müllerian ducts, whilst their caudad ends remain related to the cloaca.

The later changes in these structures vary according to the sex.

In the male the Wolffian duct persists in its entirety, ultimately forming the whole length of the excretory (seminal) channel, from the ductuli efferentes of the testis through the tubules of the epididymis, the ductus deferens, and the seminal vesicle to the ejaculatory duct. In addition it forms the prostatic portion of the urethra and the trigone of the bladder, and the ureter and collecting tubules of the kidney (*see* p. 608). The greater part of the mesonephros disappears, but traces persist and form the paradidymis (organ of Gerauldès), a small collection of tubules above the head of the epididymis. The Müllerian duct atrophies almost completely, and only a vestige remains as the minute prostatic utricle.

While the testis and Wolffian duct are migrating towards the groin, the ureter and kidney are ascending from the pelvis, and thus the two channels, the ureter and ductus deferens, come to be hooked round each other at the base of the bladder.

In the female the Müllerian duct persists, and the cephalad portion forms the uterine tube, whilst the caudad portion unites with its fellow to form the uterus, and possibly part of the vagina. The Wolffian duct atrophies (except those parts which form the ureter and the base of the bladder), but traces of it persist. Its upper portion remains in vestigial form as the epoöphoron, and its hindmost end is recognizable as a small sinus opening close to the hymen (Gärtner's duct). Rudiments of the Wolffian body persist in the broad ligament as the parovarium.

Anomalies of the Mesonephros. Abnormal persistence of mesonephric structures may lead to the development of tumours, cysts or fistulæ in later life. The commonest are cysts arising in the broad

ligaments from either the epoöphoron or the parovarium (*see* p. 711). The Wolffian body is regarded also as the origin of certain retroperitoneal cysts, and possibly of mixed tumours (adenosarcoma) in the kidney.

In a few reported cases the Wolffian duct in the female has failed to atrophy, and has persisted as a tortuous dilated retroperitoneal tract, which may extend from the lumbar region to near the hymen, discharging a puriform exudate there. In exceptional cases in males, the Müllerian duct may form a similar channel.

TUBERCULOSIS OF THE MALE GENITAL TRACT

Tuberculosis in the male genital tract commonly involves the epididymis and the seminal vesicles of one or both sides.

It is well known that tuberculous infection of the genital tract frequently complicates renal tuberculosis, and conversely infection of the genital tract often precedes a renal infection.

Much discussion has been devoted to the avenue of infection and route of spread of genital tuberculosis. On the one hand, it has been claimed that the seminal vesicle is involved primarily, either by blood-borne organisms or as a result of lymph spread from kidney and bladder; and that the disease then spreads down the vas deferens or in the lymphatics of the spermatic cord to the epididymis. There is a possibility that the prostate may be affected primarily and that later extension occurs to the seminal vesicles and the epididymis. On the other hand, there is the view, which at present is the more amply supported, that the epididymis is the primary site of the disease, being infected by the blood, and that from the epididymis the disease is carried along the vas deferens to the seminal vesicle.

In the majority of cases the epididymis is affected alone but the seminal vesicle may be affected later. Often the epididymis and vesicle of the opposite side become involved subsequently.

The Epididymis. In the earliest cases tuberculosis of the



FIG. 276. Tuberculosis of the epididymis. The globus major is replaced by a large yellow mass of caseous material. The disease has begun to infiltrate the testis, which contains numerous pin-head tubercles. There is a small chronic hydrocele with thick fibrous walls.

(Museum of Royal College of Surgeons of Edinburgh.)

epididymis is said to affect the *globus minor*, but it soon involves the entire organ. In mild cases the disease remains limited to the epididymis, and the follicles are walled in by fibrous tissue. Examination will then reveal the presence of discrete nodules, smooth, rounded and of firm consistency, perhaps half an inch or less in diameter. Such nodules may persist for years, giving rise to no symptoms.

In more severe cases the disease spreads more actively. The epididymis becomes greatly enlarged and cowl-shaped, so that the *globus major* overhangs the upper pole of the testis and partly obscures it. The tuberculous follicles coalesce until the whole epididymis is caseous. A cold abscess may then form, and spread through the adherent scrotal tissues to the surface, where it bursts and forms a sinus. Such a sinus is usually situated on the posterior aspect of the scrotum.

From the epididymis the infection commonly spreads up the spermatic cord, which becomes thickened and nodular.

The testis may escape entirely, but often it is involved extensively. Not infrequently the tunica vaginalis is infected and one form of hydrocele results.

Seminal Vesicle. The vesicle is occasionally involved in tuberculosis of the genital tract. It is enlarged and nodular, infiltrated with tuberculous follicles. Generally the disease takes a chronic form, giving rise to no symptoms, and after the epididymal infection subsides the vesicle heals. Less often a cold abscess forms, and bursts into the rectum. In some cases the disease spreads from the vesicle to the prostate.

DISEASES OF THE PROSTATE GLAND

Acute prostatitis is usually due to extension of a gonococcal infection of the urethra. It may culminate in abscess formation, and there may be extension to the seminal vesicles and the epididymis. Gonococcal prostatitis may be very intractable and may be responsible for recurring exacerbations of infection in the lower urinary tract, or for infection elsewhere in the body, especially in joints.

An acute abscess of the prostate is sometimes caused by the *staphylococcus aureus* borne in the blood stream from a lesion elsewhere. The abscess usually burrows into the urethra, but it may extend into the retroprostatic cellular tissue and reach the perineum.

After the age of fifty years (sometimes much earlier) the prostate gland may undergo hyperplastic or degenerative changes, and the effects produced are known collectively as *prostatism*, the outstanding feature of which is interference with emptying of the bladder. The pathological changes in the prostate may be considered under the following headings: (1) simple hypertrophy, (2) prostatic fibrosis, and (3) malignant disease.

Reference to the normal anatomy of the prostate is necessary for proper appreciation of the different ways in which the size, texture and relationship of the gland may be altered in these chronic diseases.

From the point of view of surgical anatomy it is convenient to regard the prostate as a fibro-muscular organ permeated by glandular tubules, situated around the prostatic urethra, and at the neck of

the bladder, with which its central part is directly continuous. The bulk of it lies behind the urethra, and this part of it is traversed by the ejaculatory ducts. The division of the gland effected by the urethra and ejaculatory ducts enables one to recognize five lobes or segments in the gland. At the sides of the urethra are the *lateral lobes*, in front is the *anterior or commissural lobe*; the triangular wedge of tissue between the urethra and the ejaculatory ducts is the *middle lobe*, and the portion behind the ducts and urethra is the *posterior lobe*.

The prostate is enclosed by a fibro-muscular *capsule* or condensation of its own substance, which sends septa into its interior. The *sheath* of the prostate is the pelvic fascia around it, and is of a firm fibrous texture; and except in front and at the apex, or lower end, it can be readily stripped from the organ. Within the sheath lies the prostatic plexus of veins, which is joined anteriorly by the deep dorsal vein of the penis. The veins lie chiefly in the groove between the bladder and the prostate. The prostatic veins enter the anterior part of the plexus, and therefore hæmorrhage is likely to occur if this part of the prostate is injured.

The lymph vessels of the prostate drain into a periprostatic plexus, from which two trunks on each side pass to the iliac and hypogastric glands.

The muscular fibres of the trigone of the bladder converge upon the prostatic urethra and are attached at the verumontanum. The anterior longitudinal coat passes into its capsule and the inner circular layer of the bladder becomes condensed upon its upper surface to form the internal vesical sphincter.

It is important to recognize that a normal prostate cannot be enucleated by subcapsular dissection, for there is no plane of separation between the capsule and the rest of the substance of the prostate. Total removal of the prostate necessitates separation of the capsule from the sheath, and as these are intimately united in front the veins of the prostatic plexus are torn. When the prostate is enucleated through the bladder, damage to the internal sphincter is inevitable, but an intra-urethral enucleation may spare the sphincter.

Simple Hypertrophy of the Prostate (Chronic Lobular Prostatitis)

This is by far the commonest cause of prostatism. The ætiology of the disease is not fully known. The changes in the prostate are very similar in nature to those found in the breast in chronic mastitis, and in the thyroid in adenomatous goitre. It is now certain that the influences which cause the changes in the prostate are *hormonic* in origin and arise in the testis. Experimentally it has been shown that male mice subjected to frequent skin applications of the ovarian hormone *œstrin* regularly develop prostate enlargement, with urinary obstruction, dilatation of the bladder and bilateral hydronephrosis. It seems probable that the action of this or similar hormones is responsible for prostatic hypertrophy in man. The likelihood is still further suggested by the finding that daily injections of *œstrin* into immature male rhesus monkeys over periods of six to twenty-eight days lead to prostatic hypertrophy in which the epithelium of the utricle (uterus masculinus)

showed very marked proliferation. The view held at present is that the testis secretes an œstrogenic substance as well as the male hormone proper, and that the normal balance between the two may be disturbed late in life, so that the œstrogenic element becomes predominant and is responsible for the prostatic overgrowth.

The outstanding change is hyperplasia of the connective tissue stroma and of the glands. The overgrowth of fibrous and plain muscle tissue may be such as to lead to fibromyomatous nodules of variable number and size. In addition, the glands usually show hyperplasia and in places may undergo cystic dilatation. Corpora amylacea are found scattered throughout the hyperplastic tissues. The microscopic appearance resembles that of a fibro-adenoma; but

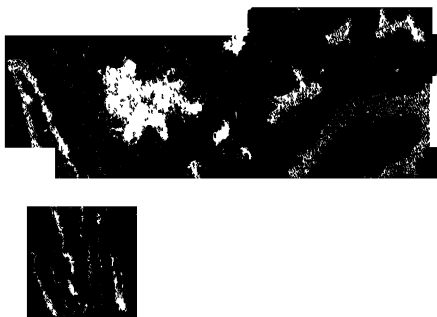


FIG. 277. Simple hypertrophy of the prostate. Glandular hyperplasia predominates.
(Laboratory of Royal College of Physicians of Edinburgh.)

as in chronic mastitis the condition is not a true tumour formation, but rather a simple epithelial hyperplasia due to some stimulus associated with physiological involution. In some cases, however, the resemblance to tumour formation may be strong, especially when the changes are restricted to a few areas of the gland. The ratio of fibrous tissue overgrowth to glandular hyperplasia varies in different cases, and the size and appearance of the gland are determined by their relative proportions. These hypertrophic changes in the prostate are commonest in the middle lobe, and may be confined to it, but, in addition, one or both lateral lobes are often affected. As a result the unaffected glandular acini are compressed and condensed along with the interglandular stroma. This compression of the normal glandular tissue is of great importance surgically, because it creates a false capsule, out of which the hyperplastic part of the prostate may be readily enucleated.

The degree of enlargement in chronic lobular prostatitis varies considerably. On an average the gland is enlarged to about twice to four times its normal size or even more, but in extreme instances it may reach the size of an orange. The enlargement is generally fairly symmetrical. Usually the gland is uniformly firm in consistency, but the consistence varies within considerable limits. When enlargement is confined to the middle lobe this portion projects into the floor of the bladder as a spherical mass or as a collar surrounding the internal meatus, which, when viewed from the bladder, has an appearance somewhat resembling the cervix uteri. It is important to recognize that enlargement of the middle lobe of the prostate cannot be detected on rectal examination.



FIG. 278. Greatly enlarged middle lobe of prostate projecting into the bladder. The bladder is greatly dilated and bilateral hydro-ureter is present.

(Museum of Royal College of Surgeons of Edinburgh.)

As a result of enlargement of the prostate there are several important secondary effects on the urethra, the bladder, and the kidneys and ureters.

Effects on the Urethra. The prostate enlarges in an upward direction owing to the resistance of the triangular ligament, and as a result the base of the bladder is carried upwards, and the prostatic urethra becomes elongated, so that an instrument requires to be passed for a greater distance than normally before it reaches the bladder. The posterior urethra may become more curved than normally, so that a catheter of special shape may be required to traverse it successfully. When enlargement of the prostate is asymmetrical the urethra may

be deflected to one side, or it may be narrowed. Often the prostatic urethra is widened from stretching of the mucous membrane over the enlarged gland.

Effects on the Bladder. As a result of obstruction to the outflow of urine from the bladder its walls become hypertrophied, and on its interior the muscle bundles become evident as prominent trabeculae, and diverticulation is common. If obstruction is of long standing the bladder becomes dilated and its walls very thin. Protrusion of the enlarged prostate into the bladder causes the orifice of the urethra to be no longer the lowest part of the bladder, and this may lead to accumulation of residual urine. The stagnation of urine predisposes to

cystitis, which is a very common complication of long-standing prostatic hypertrophy; its development is often precipitated by catheterization. Phosphatic calculi commonly develop as a result of the cystitis.

In many cases one or more diverticula are present near the base of the bladder.

Effects on the Kidneys and Ureters. As a result of prolonged distension of the bladder the escape of urine from the ureters is impeded, and they gradually become dilated. The sphincteric action normally exerted at the ureterovesical orifice is lost, and when the bladder becomes over-distended reflux of urine up the ureters occurs. The bilateral hydro-ureter is almost always associated with hydronephrosis, which in neglected cases may attain a large size, and very little kidney tissue may persist.



FIG. 279. Bladder, ureters and kidneys from a case of prostatic hypertrophy. The bladder is trabeculated, and there is a diverticulum on the side. Bilateral hydro-ureter and hydronephrosis are present.

(Museum of Royal College of Surgeons of Edinburgh.)



FIG. 280. Kidneys from a case of enlarged prostate, showing bilateral hydronephrosis and pyelonephritis.

(Museum of Royal College of Surgeons of Edinburgh.)

Subjects of prostatism frequently suffer from chronic interstitial nephritis, and the effects of this are greatly exaggerated as obstruction to urinary secretion advances. It is not surprising, therefore, that features of chronic uræmia may supervene; sometimes they completely overshadow the local effects of the prostatic disease, and they may even lead to a fatal issue without there having been disturbances referable to the lower urinary organs.

Stagnation of urine in the dilated ureters and kidneys predisposes to ascending infection from the bladder, and this usually ends fatally. Sometimes infection occurs by the blood stream and leads to acute pyelonephritis with multiple small abscesses in the kidney. *Hypertension*

Prostatic Fibrosis : Chronic Interstitial Prostatitis

In this condition the prostate gland is reduced in size and is of tough fibrous consistence, due to overgrowth of the intraglandular stroma.

The cause of the fibrosis and sclerosis is not known, but it is very probable that it is due to the same factors that in later life cause increase of the interstitial tissue of other organs such as the kidney, liver and breast.

Histologically, both the glandular tissue and plain muscle fibres appear compressed and atrophied. The gland is also the site of a round-cell infiltration.

It is important to realize that, in contradistinction to chronic lobular prostatitis, no false capsule is formed around the gland, and that the whole of the prostate is affected. As a result of the close union of the prostate to its investments no line of cleavage is present to facilitate enucleation. If enucleation is attempted it usually results in laceration of the bladder, hæmorrhage, and damage to the urethra. Therefore the treatment of prostatism of this type must be conducted on different lines from that of chronic lobular prostatitis.

In fibrous prostatitis the prostatic urethra is not elongated; in fact, it may be shortened. When the middle lobe of the prostate is especially involved an unyielding fibrous transverse bar results which causes obstruction at the outlet of the bladder. In such cases the prostatic urethra becomes shortened so that the neck of the bladder and the verumontanum are approximated. If a cystoscope is passed, obstruction is encountered at the entrance to the bladder. On inspection a transverse ridge or ledge is often noted, and the mucous membrane over it is more fixed than normally. Sometimes the fibrous bar instead of projecting as a transverse ridge presents as a firm nodule on the floor of the bladder at the internal meatus. The changes in the bladder are similar to those in prostatic hypertrophy, and are the outcome of interference with the function of the internal sphincter.

Prostatic calculi may occur, though rarely. There may be a single calculus, but more often they are multiple, and there may be a large number. They lie within cavities in the substance of the prostate, chiefly in the lateral lobes. They occur most commonly in elderly men, but have been observed in men as young as thirty years. The calculi usually have a nucleus of epithelial debris, blood clot or bacteria,

and a shell composed of mixed phosphates and the phosphates, carbonates and oxalates of calcium. They are believed to arise most commonly as a result of long-standing low-grade infection of the prostate.

Carcinoma of the Prostate

Carcinoma of the prostate may begin in an apparently healthy gland or in one which is already the site of chronic hypertrophy. It has been estimated that about 10% of prostates removed for hypertrophy show evidence of malignant disease on microscopic examination. This is undoubtedly an over-estimate. The disease occurs most often between the ages of sixty and seventy years.



FIG. 281. Metastases from carcinoma of the prostate. A very characteristic appearance of the lumbar vertebrae and pelvic girdle, when the seat of metastases from carcinoma of the prostate. The osteosclerosis is very pronounced.

In the early stage malignant disease forms multiple opaque nodules of firm texture, which render the gland unduly hard. The rate of growth of the tumour is usually slow. As the disease advances it infiltrates its capsule and sheath as well as the base of the bladder and the seminal vesicles. At a later stage ulceration of the growth occurs and leads to hæmorrhage. Spread to the retroperitoneal lymph glands is a common and early feature : involvement of the glands is found in at least 60% of cases post-mortem. Metastasis to bones is of frequent occurrence and may be obvious before urinary obstruction develops.

Histologically, cancer of the prostate often shows a glandular structure, but sometimes there is less differentiation, and the cells are arranged in irregular masses.

A type of cancer is sometimes found in the prostate which differs greatly from the above. The growth begins in the posterior lobe of the gland, and remains confined to it. The growth is small, and is of a scirrhus type, and the gland may be only slightly enlarged, but it is extremely hard. It is characteristic of this type of growth that it often gives rise to widespread metastases in the skeleton, especially in the skull, vertebræ and iliac bones, and is associated with an increase of blood phosphatase. At autopsy in such cases the primary growth may be so small as to be readily overlooked, and careful microscopic examination may be necessary to demonstrate it. The changes which may occur in the skeleton are described on p. 181. Sarcoma occasionally occurs in the prostate ; the tumour may remain encapsuled for a considerable period.

DISEASES OF THE TESTIS

Torsion of the Testis

Torsion of the testis (seldom occurs in an anatomically normal organ.) Incomplete descent, with which other structural abnormalities are often associated, predisposes to its occurrence. Torsion may occur in children or in adults, but it occurs most often about the time of puberty. It is more frequent in the right than the left testis.

The common anatomical errors of development which predispose to torsion are : (1) the presence of a patent processus vaginalis in association with incomplete descent, (2) inversion of the testis, (3) the presence of a mesorchium which separates the body of the testis from the epididymis. In many instances the testis lies more horizontally in the scrotum than normally. When a mesorchium is present the epididymis is found to be completely invested by the tunica vaginalis.

The actual cause of the torsion is uncertain, but as it has frequently followed a sudden strain or a blow, it is believed that a violent contraction of the cremasteric muscle may initiate it. It has also been suggested that a severe strain may cause a sudden engorgement of the tortuous veins of the spermatic cord sufficient to induce torsion.

The site of torsion is usually a short distance above the summit of the testis. In a few instances, where the testis and epididymis are widely separated, only the body is involved. In children the

hydatid of the testis, which is relatively large in early life, may undergo torsion alone. The extent of the twist, which occurs suddenly, varies from a half to one and a half turns, and the rapidity of changes in the organ depends on the degree of torsion. The direction of the twist is always from without inwards. Once established, the torsion is usually maintained, but occasionally it becomes undone spontaneously, but it may recur.

The changes in the testis and epididymis are due to strangulation of its blood vessels. At first, probably, only the veins are involved, with the production of venous congestion and swelling of the distal parts. When venous obstruction is long maintained thrombosis occurs, and results in hæmorrhagic infarction of the testis. The arteries may be constricted at the onset of torsion or not until later.

When examined at operation the testis and its coverings are swollen and œdematous, and have a blue discoloration from venous engorgement or thrombosis. The tunica vaginalis usually contains a blood-stained effusion. In more advanced cases the testis may have the appearance of a ripe plum, and softening from necrosis may be detected. When treatment has been delayed suppuration of the testis may ensue from superadded infection.

Torsion of the testis is usually associated with very great pain and severe shock. The abdominal muscles on the affected side are rigid, and the thigh is drawn upwards. The scrotum is usually reddened, œdematous and tender, and the testis is retracted towards the inguinal canal.

HYDROCELE

A collection of watery fluid in the tunica vaginalis may be due to disease in the testis or epididymis (secondary hydrocele), or it may arise without obvious cause (primary hydrocele).

Secondary hydrocele accompanies acute or chronic inflammation of the testis or epididymis, such as gonorrhœa, tuberculosis or syphilis, and it is sometimes associated with testicular tumours. The fluid varies in character according to the cause, and it is generally small in amount, though sometimes sufficient to mask the enlargement.

Primary hydrocele may arise at any time of life. It has been observed in infancy and it is not infrequent in old age, but it is most common during the fifth and sixth decades. The tunica vaginalis becomes distended and assumes a characteristic piriform shape. Owing to the anatomical disposition of the tunica, the testis lies below and behind the hydrocele. When the amount of fluid is great, the testis becomes flattened from pressure and may undergo a certain amount of fibrosis.

The fluid of a hydrocele is straw coloured and of watery consistency, and its amount varies from a few cubic centimetres to a litre. Its high protein content renders it valuable as a bacteriological culture medium.

Loose bodies within a hydrocele have been observed; their origin is obscure.

The cause of primary hydrocele is not fully understood. The highly albuminous character of the fluid indicates that it is not a mere transudate. In most cases, the epididymis is thickened, œdematous and somewhat congested, whilst in older patients the prostate is often enlarged and the bladder neck inflamed. On the basis of these observations some authorities regard hydrocele as secondary to a low grade infection of the whole genital system.

A *hydrocele of the cord* is a similar condition affecting a persisting portion of the processus vaginalis in the spermatic cord.

A *hydrocele of a hernial sac* is not uncommon in either femoral or inguinal hernia. It is a collection of watery fluid which forms when the orifice of the sac is occluded, and it is generally due to adhesion or impaction of the omental content of an epiplocele at the neck of the sac.

A *hydrocele with persisting processus vaginalis* is a collection of fluid in a sac communicating with the general peritoneal cavity, and it may be due to any form of peritoneal effusion. The misnomer *congenital hydrocele* is

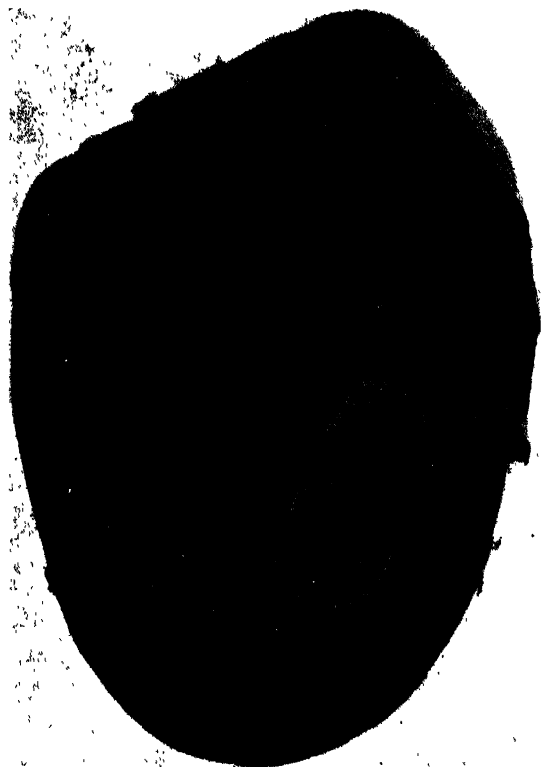


FIG. 282. Hæmatocele, resulting from hæmorrhage into a hydrocele sac. The wall of the sac is rough, and discoloured by blood pigment. The testis, which has been cut across, is compressed, and buried in fibrous tissue.

(By courtesy of Mr. J. W. Struthers.)

sometimes applied to the condition. Young persons are affected most often, for in them the processus is most apt to be patent. In such subjects the cause of the effusion is often tuberculous peritonitis. In older persons the effusion may be an ascitic collection in disease of the heart or kidneys, or it may be due to chylous ascites or malignant disease of the peritoneum.

Hæmatocele. Hæmatocele may result from a crushing injury to the testis as in vaulting, jumping, etc. Considerable shock attends the injury. The tunica vaginalis is filled with blood which may or may not clot. The surrounding tissues of the scrotum are greatly discoloured from extravasation of blood. If the blood is not evacuated from the

tunica vaginalis organisation occurs and leads to a hard and heavy swelling of the testis.

More often the hæmorrhage is attributable usually to a direct blow upon the scrotum or to injury to a vein during aspiration of the hydrocele fluid. Less commonly the hæmorrhage comes from a tumour of the testis, or it may be attributable to blood diseases such as hæmophilia, scurvy or severe anæmia.

The effused blood clots and excites an aseptic inflammatory reaction in the wall of the sac. Subsequently young blood vessels invade the clot and eventually its outer layers become organized and fibrous.

In an old-standing hæmatocele the wall of the sac is greatly thickened and indurated, and it may even become calcified. The inner surface remains rough and shaggy, and discoloured by blood pigment. The testis becomes embedded in the new fibrous tissue, and may be almost indistinguishable.

CYSTS AND TUMOURS OF THE EPIDIDYMIS

Cysts in connexion with the epididymis are common; they may be small and multiple, but more often are single.

Multiple cysts are usually situated in the head of the epididymis, less often in the body or the tail. The condition occurs in middle-aged men, and is often bilateral. The cysts vary in size, but they are seldom larger than a pea; they are thin walled, tense and firm, and contain transparent or turbid fluid, in which there may be spermatozoa. The origin of the cysts is uncertain: they are said to arise either in remains of the Müllerian duct or from dilatation of the tubules of the epididymis.

Single cysts are more common and may occur in early adult life. The cyst may be unilocular or multilocular and may attain the size of an orange. It is usually situated outside the tunica vaginalis but may be within it and arises either between the globus major and the body of the testis or above the epididymis. As the cyst increases in size it separates the epididymis from the body of the testis, and the vasa efferentia may be stretched over the cyst.

The wall of the cyst is fibrous and often thick, and is lined with columnar or flattened epithelium. The cyst contains opalescent milky fluid of alkaline reaction, which on standing separates into two layers, the upper clear and the lower milky; it contains lymphocytes, fat globules, epithelial cells and spermatozoa. In most examples a communication between the cyst and a seminal tubule may be demonstrated. In some cysts the fluid is clear and no spermatozoa are present.

In the majority of instances a cyst of the epididymis arises from rupture of one or more of the vasa efferentia at the hilum of the testes. It is likely that others originate in vestigial remnants similar to cysts of the broad ligament. Thus it is believed that a cyst may arise from the hydatid of the testis (Morgagni), *i.e.*, from remnants of the Müllerian duct, from the paradidymis (organ of Giralès), *i.e.*, remains of the Wolffian body, or from the vasa aberrantia—normal diverticula of the inferior end of the ductus deferens.

Tumours of the epididymis are very rare. Simple tumours, such as lipoma, fibroma, adenoma and leiomyoma, which are the natural outcome of the anatomical structure, have all been encountered. They are seldom larger than a walnut. Sarcoma of either spindle, chondromatous or melanotic type has been observed in a few instances.

A carcinoma may arise from the epithelium lining the tubules. It has been observed most frequently in early adult life, is usually small, irregular and nodular and may be mistaken for chronic inflammatory enlargement of the epididymis. It may extend along the spermatic cord and may involve the coats of the scrotum. The tumour, though usually small, is very malignant, and metastasis to the retroperitoneal glands and the lung is common. Microscopically, epithelial tumours of the epididymis are generally of adenocarcinomatous or rarely of squamous-cell pattern.

SYPHILIS OF THE TESTIS

The epididymis on one or both sides may be enlarged temporarily during the florid stage of syphilis. Enlargement is confined to the globus major and is painless and may therefore be unnoticed. Probably the underlying cause is an inflammatory affection of the tubules.

Since the institution of effective methods of treatment of primary syphilis, tertiary lesions, formerly common in the testis, are now seldom observed; but when they occur they almost always involve the body and its investing tunica.

Subjects of inherited syphilis may develop orchitis, which is usually bilateral. It is commonest in infancy or in the second or third year, and syphilis is the only common cause of testicular enlargement in early life. The testis is usually about the size of a pigeon's egg and is hard and painless. The orchitis may be very indolent, but very seldom culminates in gumma formation. When occasion for pathological examination has arisen, it has been noted that the connective tissue between the tubules has been greatly thickened and invaded by lymphocytes and plasma cells.

In adults suffering from acquired syphilis the testis, usually of one side only, may be the seat of chronic enlargement, especially after the second to fourth year following infection. The disease may take the form of diffuse interstitial orchitis or be of a gummatous character; but a combination of the lesions is more common.

In the diffuse form there is moderate enlargement of the testis of gradual and painless onset. The testis may retain its normal shape or become spherical. It is hard and woody and is generally devoid of sensation. There is often an effusion of serum within the cavity of the tunica vaginalis, seldom amounting to more than two or three ounces. Later the tunica vaginalis may be obliterated by adhesions. The tunica albuginea may be the seat of nodular thickening but the epididymis is unaffected. The substance of the gland is infiltrated by newly formed connective tissue disposed radially from the rete testis; and, when cut, the testis retains a flat surface as the tubules

are restrained by the fibrous infiltration. Occasionally there is a small central gumma, and less often multiple areas of degeneration. In untreated cases the secretory tubules may be extensively destroyed and atrophy of the testis may ensue.

The appearance of the testis varies according to the stage of the disease and the amount of fibrous infiltration. There may be a single homogeneous yellow necrotic mass in the centre of the greyish-red glandular and opaque fibrous tissue, which may increase until the entire testis is involved; or there may be multiple small areas of degeneration amidst a granulomatous and enlarged testis; such areas usually coalesce and may destroy completely the secretory tubules. From extension of the syphilitic process the scrotal tissues may be infiltrated, so that finally the skin and dartos muscle may be involved. Rupture on the skin surface may lead to a typical sloughing syphilitic ulcer, or the diseased testis covered by a fungous mass of granulations may project on the surface with the scrotum retracted around it. The testis may herniate to such an extent that scarcely any part of the organ is contained within the integuments of the scrotum.

|| TUMOURS OF THE TESTIS

Few subjects in surgical pathology have given rise to such difficulty in classification and interpretation as that of testicular tumours. The difficulty was the outcome of the complex histopathology of these tumours and of the error of drawing conclusions from an examination of only a limited portion of a tumour. Now it is insisted that examination of many parts, preferably by the large section and by special methods of staining, is essential if all the components of the tumour are to be classified correctly. Even with these refinements the nature of the tissues may be difficult to define. Careful investigation of large series of cases has helped to dispel some of the confusion that has existed and, as a result, the older nomenclature and classifications, which were either misleading or cumbersome, have been revised and simplified. Two well-defined groups are now recognized: (1) The teratoid or mixed tumour, and (2) the germinal cell tumour (the commonest), variously known as seminoma or semino-carcinoma (spermato-cytoma); the first is the common title. There is in addition a very rare type of tumour which originates in the interstitial tissue of the testis (3) interstitial-cell adenoma.

General Features of Testicular Tumours

Most tumours of the testis are malignant or potentially malignant and develop in adult life; a few, such as the teratomatous cysts, may be present at birth. In rare instances the disease attacks both testes simultaneously, or the remaining testis may be affected some time after orchidectomy. Malignant disease may attack a retained or ectopic testis, but it remains uncertain if either of these maldevelopments increases the liability to malignancy, although Gordon Taylor

found maldescent present in 15 out of 50 cases observed by him. A history of injury in relation to the occurrence of the tumour is present in almost 20% of instances. The tumour may be very small or may attain large dimensions, sometimes rapidly after a long period of latency. The initial site of the tumour (particularly the teratoid variety) is usually the mediastinum of the testis, deep to the tunica albuginea, and as growth proceeds the testis is gradually compressed so that finally it may appear as a wafer at the periphery of the tumour, or it may be incorporated in the tumour. The epididymis remains long unaffected. A small hydrocele or hæmatocele may be present, especially after injury.

The urine from subjects of testicular tumour contains gonadotropic hormones which are responsible for the positive Aschheim-Zondek reaction. (In most the hypophyseal hormone predominates, in a few a chorionic hormone. The hormone output is higher in seminoma than teratoma, and greater in embryonal adenocarcinoma and highest in chorionic carcinoma. The test, both qualitatively and quantitatively, may be of great value in diagnosis and prognosis. A seminomatous type of tumour associated with an increased excretion of hypophyseal hormone is radio-sensitive and the prognosis is relatively good. In tumours associated with an output of chorionic hormone the prognosis is poor because the tumour is resistant to irradiation.

(After removal of a seminoma the hypophyseal hormone continues to be excreted in excess.

Secondary growths from testicular tumours may result from invasion of lymph vessels or of veins. Lymph-borne metastases are usually noted first in the lumbar glands; the inguinal glands are not affected unless the tumour has involved the wall of the scrotum. Blood-borne metastases are common in the lungs, and may be present later in other organs.

The Teratoid Group of Tumours

A teratoid tumour usually appears between the ages of twenty and thirty years. It may be smooth or lobulated, soft or hard; at first its growth is limited by the resistance of the tunica albuginea, (so that for long the enlarging testis retains its shape.) It may give rise to an effusion of clear or gelatinous fluid in the tunica vaginalis, but the effusion is seldom considerable and is not bloodstained unless injury (as from exploratory puncture) has occurred.

On section the testis may be obvious at the summit of the tumour; it may appear normal, but more often it is compressed and appears as a narrow strip of tissue separated from the tumour by a condensed fibrous layer or capsule (see Fig. 282). The tumour may be homogeneous, but frequently it shows areas of hæmorrhage or necrosis or cystic spaces containing gelatinous material. Cartilaginous nodules are often present, and may be so abundant that the tumour has the appearance of a chondroma.

Microscopically, the most arresting feature of a teratoid tumour is its complexity. The tissues may be of great variety and may be

mature or embryonic, and it may be impossible, especially in the case of atypical glandular structures, to specify their character. In some examples differentiation may occur to a remarkable degree and a part of an entire adult organ may be reproduced. But generally the tissues are disposed in a haphazard manner without more than slight attempts at specific associations.

Occasionally one of the component tissues occurs in great preponderance and may appear to suppress others. There are, for example, rare tumours of the testis which have the appearance of chondroma, fibroma, adenoma, etc., but which can be shown by more thorough examination to be teratoid tumours in which one type of tissue preponderates. The teratomatous cyst and chorionic carcinoma described below are examples of such one-sided growth, in these cases the ectodermal elements.

For descriptive purposes it is convenient to catalogue the many tissues which may be found in testicular teratomata according to the germ-layer—ectodermal, entodermal, and mesodermal—to which they may be assigned; and, on this basis, the following table indicates the tissues which may be represented.

<i>Ectodermal</i>	<i>Entodermal</i>	<i>Mesodermal</i>
Stratified squamous epithelium, with or without keratinisation.	Glandular tissue of intestinal type, sometimes with mucus-secreting cells.	All gradations of young fibroblastic tissue.
Hair.		Myxomatous tissue.
Neuro-epithelium, which may assume acinar or papillary formations almost indistinguishable from glandular structures.	Glandular structures, sometimes unspecific but often identical with the thyroid, the salivary glands or liver.	Fat.
Melanin-pigmented cells.	Ciliated epithelium resembling the bronchial mucous membrane.	Lymphoid tissue.
Trophoblastic epithelium.	Renal tissue, with glomeruli.	Muscle fibres, especially plain.
		Hyaline cartilage.
		Bone, sometimes with hæmopoietic tissues.

A testicular teratoma may be composed of a few or a complexity of the above tissues. Superficially they may appear to be disposed in no particular order, but none the less, there is often a suggestion of correlation of particular tissues. For example, it is very noticeable that glandular epithelium, especially of intestinal type, is often associated with young mesenchymatous tissue in which there may be plain muscle fibres and aggregations of lymphoid tissue. Epithelium like that of the respiratory tract is often found in proximity to bars or nodules of cartilage. Embryonic tissues of the nervous system may occur alongside tissues resembling nerve-sheath elements or a meninx-like sheath. In association with squamous epithelium there may be hair follicles, arrectores pilorum, sebaceous material and fat. Probably these specific associations connote an abortive attempt at reproduction of adult structures and are identical with the correlation of tissues which occurs in early development.

Some teratomata of the testis present such characteristic features as to warrant more detailed consideration.

Tri-dermal Teratoma (Fibrocystic Disease). This is one of the commonest types: it usually grows slowly, and may appear to be benign. On section its appearance varies according to the relative proportion of cysts, fibrous tissue and cartilage. Areas of softening and degeneration are often present in some part of the tumour. Microscopically, a great variety of tissues may be present, but the predominating elements are cysts lined by any type of epithelium, stroma which is very cellular and of embryonic type, and a variable quantity of hyaline cartilage.

From the pathological side it is important to recognize the great malignancy of the tumour. All the tissues may participate in this activity in different degree, but very commonly the glandular elements show the most active proliferation.

Teratomatous or Dermoid Cyst.

This is the rarest testicular teratoma; it resembles in all respects, except size, the common ovarian teratomatous cyst (*see* p. 706). The tumour is present at birth, and grows very slowly. Morphologically, it represents excessive epiblastic overgrowth in a teratoma.

The tumour is cystic and loculated, is lined with stratified epithelium, and contains sebaceous material and hair. Part of the tumour is usually solid, and this portion usually contains cartilage, bone, and nerve elements. Malignant transformation seldom occurs in this type of tumour, but it is not unknown.

Chorionic Carcinoma. This tumour, which is probably morphologically identical with chorion-epithelioma of the uterus, is relatively rare. The tumour is usually small and, on that account, may be overlooked; it is soft and is very liable to necrosis and hæmorrhage, and spontaneous retrogression has been observed. Microscopically, it is composed



FIG. 288. Teratoma testis with involvement of skin of scrotum and secondary deposits in the inguinal glands. The body of the testis is stretched over the surface of the tumour.

of syncytial masses and cells so arranged as to resemble trophoblastic tissue.

The syncytial epithelium has the property of eroding blood vessels, and thus causes extravasation of blood; for the same reason it usually gives rise to metastases in the lungs, and later in the liver. The (secondary growths appear as hæmorrhagic tumours, which may become very large.) Histologically, the metastases may vary considerably and present structures which are characteristic of a teratoma.

A chorionic carcinoma may be responsible for breast activity in the

male and the pronounced Aschheim-Zondek reaction indicates a high prolactin output.

Malignancy and Metastases in Teratoid Tumours. Teratoid growths, according to all standards, are extremely malignant. Survival beyond three years after the appearance of the tumour is exceptional. It is important to realize that a teratoma may give rise to metastases and death while the primary tumour is still small; but in most cases the features of malignancy are evidenced by fairly rapid increase in size of the testicular swelling and by invasion of the scrotum.

In the majority of teratomata malignancy is a property of the whole tumour and shared by several or all of its component tissues, though not always in equal degrees. Formerly malignancy was ascribed to exaggerated growth of one component, but this view is erroneous. In the majority metastases occur in the lumbar glands. The gland enlargement may result in a very bulky confluent tumour. Occasionally

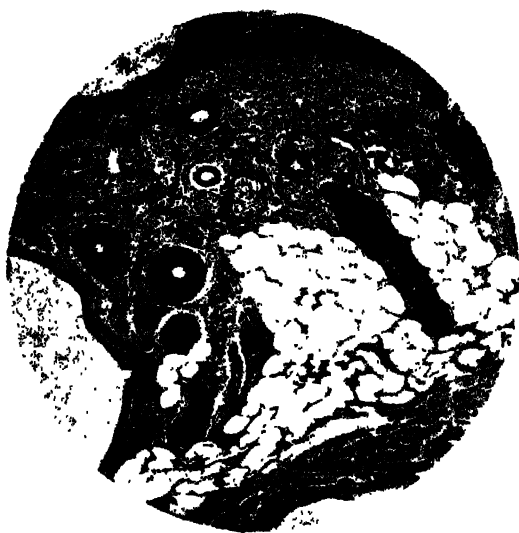


FIG. 284. Portion of testicular teratoma, showing skin, hair follicles, sebaceous glands, and fat.

(Laboratory of Royal College of Physicians of Edinburgh.)

the supraclavicular glands on the left side are involved, probably as a result of invasion of the thoracic duct by cancerous emboli.

Spread by the blood stream is common and is a specially notable feature of chorionic carcinoma.

The structure of the metastases is almost as complex as that of the primary growth, they usually contain two or more of the cellular constituents of the parent tumour. They may show greater differentiation than the primary growth, but usually the reverse obtains. It has been alleged that the metastases may contain tissues not present in the primary growth, but this assertion is probably erroneous and based on an insufficiently thorough examination of the primary tumour.

The Origin of Teratoid Tumours of the Testis. There are many speculations on this subject, and until our knowledge of the origin of teratomata in general is on a more sure foundation dogmatic statements are scarcely permissible. Probably careful examination of very early cases might help to clear up some of the doubts.

Following the theory of Cohnheim that tumours arise from



FIG. 285. Seminoma of the testis. Note the coagulated fluid in the tunica vaginalis.

(Department of Surgery, University of Edinburgh.)

"embryonic rests," it has been suggested, without much confirmation, that teratoid tumours arise from remnants of the Wolffian body. Others have suggested that they arise from ordinary sex or germinal cells by a process analogous to parthenogenesis, and that therefore a teratoma represents a distorted foetus; this theory, though superficially adequate, has not been upheld. Marchand and Bonnet advanced the hypothesis that a testicular teratoma might be derived from an isolated blastomere detached from a segmenting ovum very early in cleavage. This last view may account for some extragenital teratoma, but it fails to account for their great predilection for the ovary and testis.

As teratoid tumours grow from the region of the rete testis, where

developmental errors would be most expected, it is believed that they arise from primitive undifferentiated cells with pluripotent characters, that originally arose in the mesothelium of the genital ridge but failed to develop or to become connected with the secretory tubules of the testis.

The exciting cause of the neoplastic development is not definitely known, but trauma appears to play an important part.

The Seminoma Group of Tumours

This is the commonest tumour of the testes. It may occur at any period of adult life but is commonest between the ages of twenty and forty. The tumour probably arises from the germinal epithelium of the secretory tubules of the testis; it

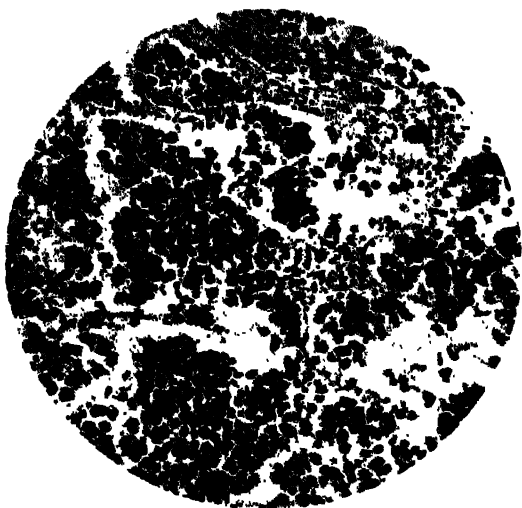


FIG. 286. Seminoma of the testis.
(Laboratory of Royal College of Physicians of Edinburgh.)

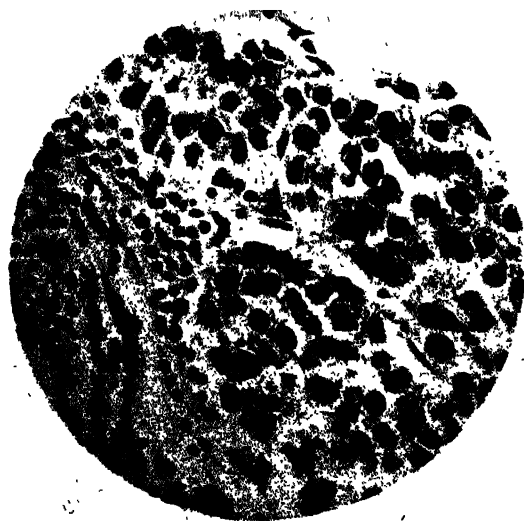


FIG. 287. High power of same section as in Fig. 286.
(Laboratory of Royal College of Physicians of Edinburgh.)

grows more slowly than teratoid tumours and, on an average, reaches the size of a closed fist within two years. The tumours (and the metastases) are very radio-sensitive.

In shape the tumour is spherical or ovoid. It is firm and solid, and, except for areas of hæmorrhage or of degeneration which are often present, it is of a homogeneous consistency. The cut surface is fleshy or gelatinous, and is intersected by fibrous septa which may produce an appearance of lobulation.

The epididymis may be uninvolved, fused to the tumour, or indistinguishable.

Microscopically, tumours of this class show considerable individual variation, and even in the same tumour the appearances may not be uniform. In some tumours the cells are large with clear cytoplasm, and resemble the spermatocytes of the testicular tubules; in others the cells are smaller, with darkly staining nuclei and much less cytoplasm; while in others the cells resemble lymphocytes. Like the cells of the normal testis, the tumour cells are often markedly eosinophilic. The cells are usually arranged in sheets or bands and mitotic figures may be numerous. An embryonal adenocarcinomatous type sometimes occurs. A characteristic feature is the presence of small lymphocytes embedded in small or large groups amongst the epithelial cells. The blood vessels, as in other carcinomata, are often well formed, but in many instances they are thin walled and of embryonic type.

In some examples there is evidence of marked anaplasia and the features of a carcinoma and of a sarcoma are blended—*carcino-sarcoma*. Usually the cells are mostly of a carcinomatous character, but, in addition, there are large, round, oval or spindle types, suggestive of sarcoma.

Tumours of the seminoma group metastasize chiefly by the lymph vessels, but occasionally they behave like a sarcoma and give rise to secondary growths in the lungs.

Origin of the Seminoma Group of Tumours. It is generally admitted that these tumours resemble anaplastic carcinoma in other glandular organs and that they are derived from precursor cells of the spermatogonium of the testicular tubules—"embryonal carcinoma." This is borne out by the observation that it is sometimes possible to trace transitions between normal and almost normal seminiferous tubules and frankly malignant tissue; and, in addition, the cells are usually so specific in type that a common origin is the more likely. Nevertheless it must be stated that some observers have attempted to explain the origin of the tumour on the basis of a one-sided development in a teratoid tumour.

Interstitial-cell Tumour. This is a very rare tumour. It is of adenomatous type and affects the body of the testis: it is small in size and lightly encapsuled and traversed by fine trabeculae which render it lobulated. Its special feature on cross section is its brown colour. Malignant change with metastases has occurred in a few examples. The Aschheim-Zondek test may be positive, and features related to an excessive output of oestrogen have been noted. Histologically, as would be expected from its origin, it shows disorderly solid masses of polygonal cells in lobular formation. The cells have a granular and particularly acidophilic character.

The tumour should be regarded as a very rare cause of innocent testicular enlargement.

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CHAPTER XXXIII

DISEASES OF THE FEMALE GENERATIVE ORGANS

PHYSIOLOGY OF MENSTRUATION

THE phenomena of the menstrual cycle and their relation to other sexual and reproductive processes constitute interesting biological problems, and are so closely linked to the functional activity of other endocrine glands as to have an importance in general pathology. Until comparatively recently the outlook upon the whole subject was to a large extent speculative, but within the past few decades experimental and clinical research has done much to establish it on a scientific basis.

The Menstrual Cycle. The menstrual cycle may be divided into four phases :—

- (1) Premenstrual hypertrophy.
- (2) Menstrual flow.
- (3) Post-menstrual involution.
- (4) Interval.

Throughout the whole menstrual cycle, and from puberty to the menopause, the uterine mucous membrane is never at rest. It is constantly under the influence of hormones derived from the ovaries, the pituitary gland, and other organs, and is maintained in a continual state of activity.

(1) *Premenstrual hypertrophy* of the uterine mucosa begins a week or ten days before the onset of the menstrual flow. It is characterized by a gradually increasing hyperæmia with great proliferative activity of the cells of the endometrium, which becomes twice or even three times its normal thickness. The changes resemble those of the decidua formation of early pregnancy, and they affect the stroma, the mucous glands and the blood vessels of the endometrium. The stroma cells proliferate and separate into two more or less well-defined layers, a superficial compact layer in which the cells lie closely opposed, and a deep spongy layer in which they lie separated by œdema. The epithelial cells proliferate, and mitotic figures may often be demonstrated. The cells lining the mucous glands are particularly affected, and the glands become dilated, elongated and tortuous. Often the proliferation is so great that the epithelium projects into the lumen of the glands in the form of multiple tuft-like processes. Capillary dilatation is an important feature, and in the later part of the premenstrual phase it becomes very evident. Immediately before the beginning of the second phase the capillary walls rupture and give rise to minute hæmatomata under the epithelium.

(2) *The menstrual flow* results from hæmorrhage from the dilated capillaries. The blood collects in the stroma of the endometrium and is then discharged with small portions of the epithelium. Along with the blood there is a free discharge of mucoid secretion from the glands. At one time it was believed that the greater part of the endometrium was cast off, but this view is probably erroneous, and in normal circumstances the loss of tissue is minimal.

(3) *Post-menstrual involution* is characterized by retrogressive changes in the endometrium. The blood vessels return to normal size, relief of œdema and congestion allows the membrane to shrink to its former thickness, the effused blood is absorbed and the proliferated cells atrophy and disappear. The glands in collapsing assume a tortuous or plicate arrangement, which in microscopic sections may give a confusing picture, as of acini within acini.

(4) *The interval* is of short duration. During this period the endometrium enjoys a period of relative quiescence, and any physiological loss sustained during the active phases is made good. It is important to note that the endometrium is never in a true resting phase. The phase of repair merges with that of renewed activity, and in microscopic section the features of the two phases are often blended.

Relation of Menstruation to Ovulation and Reproduction. It has long been recognized that there must be a close relationship between ovulation, the process whereby the mature ovum is discharged from its follicle at the surface of the ovary, and the cycle of menstrual changes, but the nature of the relationship has proved difficult to determine. Opportunity for observation of the behaviour of healthy ovaries is rarely obtained, and research upon animals is complicated by the circumstance that few animals menstruate, and that the œstrus cycle in animals is not the counterpart of the human menstrual cycle.

It is believed, however, that in women with regular menstrual cycles, ovulation occurs regularly once a month, and it precedes and determines the menstrual flow. The time relationship of menstruation and ovulation has been studied by correlating the menstrual histories of gynæcological patients with the appearance of mature or newly ruptured follicles in the extirpated ovaries, and from these observations it seems probable that ovulation occurs thirteen or fourteen days before the menstrual flow, that is, shortly before the commencement of the phase of premenstrual hypertrophy.

Modern views in regard to the significance of menstruation emphasize the especial importance of the stage of premenstrual hypertrophy. It is believed that this process is designed to prepare the uterus for possible pregnancy, and that if pregnancy occurs the endometrial hypertrophy passes insensibly into decidua formation. If fertilization is not achieved the hypertrophic state being superfluous comes to an end, and the menstrual flow begins. Thus the menstrual flow is not a preparation for possible pregnancy but an indication of failure to conceive.

Ovarian Hormones. The ovary exerts a hormonal control over the whole cycle of menstrual changes, for removal or destruction of the ovaries invariably produces an "artificial menopause."

In recent years it has been demonstrated that there are at least two types of ovarian hormone, derived respectively from the Graafian follicle and the corpus luteum.

The follicular hormones are *œstrone* and the much more active *œstradiol*; the luteal hormone is known as *progesterone*.

œstrone is a fat-soluble substance which can only be administered by injection. It has now been obtained in crystalline form, and has been shown to be a condensed carbon-ring compound consisting of four linked aromatic rings. Its chemical constitution is closely allied to that of the carcinogenic hydrocarbons present in coal tar (*see* p. 67). *œstrone* can be isolated from the liquor-folliculi and from other parts of the ovary and also from the placenta. It is present in large amount in the urine of pregnant animals, especially the mare. It is found in greatest quantity, remarkably enough, in the urine of the stallion. *œstrone* determines the onset of the menstrual flow and probably controls the onset of puberty and the development of secondary sexual characters. The administration of *œstrone* accelerates puberty in immature animals, induces "heat" after spaying, and hastens the reappearance of "heat" in the lactation period.

Progesterone is secreted by the corpus luteum and, during pregnancy, by the trophoblast. It tends to stimulate endometrial hypertrophy and, in association with *œstrone*, to prevent the menstrual flow. Shortly after the corpus luteum appears in a ruptured Graafian follicle it determines the onset of premenstrual hypertrophy. If fertilization occurs the corpus luteum grows, and by stimulating decidua formation ensures the implantation of the ovum. If fertilization fails to occur the corpus luteum soon degenerates and its secretion ceases. The sudden withdrawal of the two hormones, *œstrone* and *progesterone*, then determines the destructive endometrial changes which lead to the menstrual flow.

In addition to the menstrual effects, both *œstrone* and *progesterone* have an influence on hypertrophy of the breast and on lactation.

The ovarian hormones, both *œstrin* and *lutein*, are under the hormonal control of the anterior lobe of the pituitary gland. It has been shown that removal of the anterior pituitary in immature animals inhibits the development of the ovary and also of the secondary sexual characters; in adult animals it inhibits ovulation; if ovulation has occurred, it inhibits the formation of corpus luteum; and if the animal is pregnant it brings about abortion. Thus the pituitary controls all phases of ovarian activity. It exercises this control through the agency of the gonadotropic hormone *prolan*, which may contain two distinct principles, *prolan A* and *prolan B*, the former effecting maturation of the follicle, the latter formation of the corpus luteum. *Prolan* or a similar substance is excreted in the urine of pregnant women, and the demonstration of its presence forms the basis of the Aschheim-Zondek test. It is interesting to note that *prolan* or a similar substance is present in large amount in the urine of men suffering from tumours of the testis.

ACUTE ENDOMETRITIS

By far the most important type of endometritis is that which occurs after abortion or in the puerperium, and it overshadows all others in both virulence and gravity.

Gonococcal endometritis is common, but is never very acute, and is usually obscured by the more obvious effects of gonorrhœa upon the urethra, cervix and uterine tubes. Occasionally acute endometritis follows the use of infected instruments for minor operative procedures. Rarely the infection is blood borne, and it may occur in the course of zymotic diseases, acute tonsillitis, and analogous affections.

Puerperal Endometritis

The uterus owes its great susceptibility to puerperal infection to the presence of the large placental site composed of spongy decidua without epithelial covering. This forms an ideal nidus for bacteria, and its large blood vessels closed only by recent clot provide a ready avenue by which infection may reach the blood stream.

It was formerly the custom to distinguish two types of this disease, (1) putrid endometritis due to saprophytes, and (2) "septic" endometritis due to bacteria capable of invading living tissues.

It is now generally acknowledged, however, that this classification is somewhat artificial, for saprophytes rarely exist alone, and parasitic organisms may possess any degree of virulence.

In general, two main types may be recognized :—

(a) Surface infection of the uterine wall.

(b) Deep infection of the uterine wall.

(a) *Surface Infection.* In the mildest forms of endometritis the effects are those of a localized inflammatory process. The endometrium is covered with soft, dirty sloughs and bathed in foul purulent lochia, and the uterus is enlarged, œdematous, and flabby from toxic paresis. Microscopically, the most striking feature is the great vigour of the reaction. Bacteria and necrotic areas are surrounded by healthy leucocytes, which form dense barriers and effectively prevent invasion of the deeper tissues.

(b) *Deep Infection.* In its more severe forms the disease resembles a spreading cellulitis. Sloughs are present on the surface, but the exudate is somewhat thin and often scanty. Microscopically, the organisms are seen penetrating deeply amongst the muscle fibres, which are œdematous and degenerated. Polymorph leucocytes are relatively scanty, and the infection is not circumscribed in any way.

Complications. The great danger of puerperal sepsis lies less in toxic absorption from the uterus than in the risk of spread of the infection to other parts.

One of the commonest complications is cellulitis of the connective tissues of the parametrium and broad ligaments. This may arise by direct extension of the disease through the uterine wall, but it is due far more commonly to direct access of the organisms through a laceration of the cervix uteri.

Peritonitis may occur, either by spread of the infection along the tubes or, rarely, as a result of rupture of the uterus during delivery. Peritonitis is generally due to infection with hæmolytic streptococci, and is always of grave import.

Thrombophlebitis of the uterine and pelvic veins is another complication of extreme gravity, for after childbirth the veins are large and tortuous, and many are filled with soft, recent blood clot. The infected clot is very apt to disintegrate, with subsequent septicæmia and pyæmia.

The Infecting Organism. In acute fulminating forms of puerperal sepsis the causative organism is almost invariably a hæmolytic streptococcus, usually of the type labelled "pyogenes." According to Colebrook and Howe, an anaerobic streptococcus is not infrequent: *B. coli* often coexists, less commonly *B. pyocyaneus* or other organisms. In milder forms of the disease the organisms are varied. *B. proteus* and other saprophytes are common, and may be accompanied by non-hæmolytic streptococci.

The Source of Infection. This is the fundamental problem of puerperal sepsis, for upon the answer to it depends the whole campaign of prophylaxis. Is the infecting organism present in the vagina before parturition? is it present in some distant focus, whence it may reach the uterus in the blood stream? does it ascend the genital tract from the vulva, perhaps assisted by the examining finger or an instrument? or is it quite exogenous, and brought to the uterine mucosa through some unrecognized breach of technique?

The bacterial flora of the vagina in late pregnancy and the puerperium has been investigated by many workers in recent years, with surprisingly regular findings. In late pregnancy pathogenic organisms are present in approximately 50 per cent. of cases. Streptococci occur in a large proportion of these cases, but they are practically always non-hæmolytic, and streptococcus pyogenes is very rare. Non-hæmolytic streptococci are found also in the uterus after parturition, but, although they may lead to mild forms of endometritis, they have no relation to severe puerperal sepsis.

Hæmatogenous infection from distant foci, such as the teeth or tonsils, must be seriously considered as a cause of puerperal sepsis, for this disease may occur in healthy women, exposed to no exogenous infection, after a normal, spontaneous, unassisted delivery. But this source of infection can only apply to a small proportion of cases.

It seems likely that infection from the vulva is commoner than is generally supposed. The vulva, with its folds and crevices, its innumerable hair follicles, and its close proximity to the anus, must always be infected to some degree.

Lastly, there can be no doubt that exogenous infection occurs, and indeed it may be of paramount importance. Formerly the contagious nature of "puerperal fever" was well known, and in lying-in hospitals a single case might infect a whole ward. The danger of such epidemics is now almost past, but even with every possible care there are occasional instances of case-to-case infection. The most tragic feature of such exogenous infections is their great virulence. After transmission from

one patient to another the streptococcus attains such intense pathogenic properties that the disease is often fulminating.

Further evidence of the importance of exogenous infection is found in the incidence of puerperal sepsis, which is especially apt to occur in primiparæ, in abnormal labours, or in any circumstances in which the passages are bruised, the cervix lacerated, the perineum torn. The risk is greatest of all, moreover, when any form of intervention becomes necessary, especially the manual removal of the placenta.

CHRONIC CERVICAL ENDOMETRITIS (Cervical Erosion)

The cervix uteri is lined on its inner aspect by mucous membrane similar to that of the body of the uterus, but with somewhat taller columnar epithelial cells and more numerous mucous glands. On its outer (vaginal) aspect it is covered by squamous epithelium continuous with that of the vaginal fornices. The mucous membrane of the cervical canal is of deep red colour, the external squamous covering is pale pink, and the junction of the two is situated exactly at the external orifice.

In a cervical erosion the appearance is quite different, for the deep red mucosa transgresses its normal limits and appears on the vaginal aspect of the orifice as an irregularly rounded area the colour of a ripe strawberry. The surface of the area is unbroken (there is no true erosion or ulcer), and it may be smooth or slightly granular. Not infrequently it is studded with small bluish cysts (Naboth's ovules), which result from dilatation of the mucous gland acini. Laterally the "erosion" merges gradually, in an ill-defined line of transition, with the surrounding squamous epithelium.

Microscopically, the surface is usually covered by columnar epithelium, but this may later become replaced in patchy fashion by squamous cells. Deep to the epithelium there are numerous glands like those of the normal cervical endometrium, but more complex in structure and more closely set. Collections of lymphocytes and plasma cells are present in the strôma.

Chronic cervical endometritis usually occurs as a sequel to gonorrhœa or to the low-grade infection of a laceration of the cervix, but it may develop when there is no evidence of previous disease, and it is not unknown in virgins. On this account it has been suggested that the condition is not infective but is a simple overgrowth of glandular tissue. There is, however, but little support for this view, and there seems little doubt that the condition is a result of chronic infection, aggravated perhaps by the irritative effect of the acid vaginal secretion upon exposed endometrium. Bacteriological examination usually reveals the presence of more than one organism, and this is not surprising in view of the varied bacterial flora of the vagina. Streptococci, hæmolytic or non-hæmolytic, are common, and coliform bacilli, diphtheroids and staphylococci may be present. That elusive organism, the gonococcus, dies out so quickly and is cultivated with such difficulty that it can rarely be demonstrated, but its causative influence may sometimes be suspected.

CHRONIC CORPOREAL ENDOMETRITIS

Chronic corporeal endometritis may occur as a sequel of definite acute or subacute infections, such as puerperal sepsis or gonorrhœa, or it may occur in women who have had no previous uterine disease, and may even be found in virgins. Two main types may be recognized; (1) the hypertrophic type, (2) the atrophic type. Atrophic endometritis is not uncommon in elderly women, and may then be recognized as a distinct type, the senile type. Rarely tuberculous endometritis occurs.

(1) **The Hypertrophic Type.** In this condition the principal changes occur in the mucosa of the body of the uterus, but the cervical endometrium may be affected to a limited extent. On naked-eye examination the most striking feature is the great thickness of the mucous membrane, which is soft, velvety and congested. Often the whole mucous surface is covered with small raised nodules, and sometimes larger elongated or polypoidal masses project into the lumen.

The increased thickness of the mucosa is due principally to great hypertrophy of the glands, which become elongated and very tortuous. The epithelial cells proliferate and increase in size and become distended by mucus to goblet shape. The acini may be dilated with retained secretion. Thus the condition is somewhat similar to that of the physiological proliferation of the premenstrual period. Sometimes the glandular proliferation is so extensive as to suggest a neoplastic change, and indeed the condition has sometimes been termed "benign diffuse adenoma." The stroma of the mucous membrane usually presents the signs of chronic inflammation, and is infiltrated by granulation tissue with lymphocytes and plasma cells, but in some cases inflammatory cells are scanty or absent and the stroma is fibrous. The blood vessels are often thick walled and partially occluded by fibrosis.

Hypertrophic endometritis was formerly regarded as the result of infection of the uterus, but the frequent absence of histological evidence of inflammatory change cannot be ignored, and the condition is now believed to result from proliferative activity of the endometrium associated with endocrine dysfunction.

(2) **The Atrophic Type.** This condition is most common after the menopause (senile type), but it may occur at an earlier age. It differs from the hypertrophic type in that the endometrium is not thickened by the overgrowth of glands and stroma, but is thin and atrophic. The epithelial cells on the surface and those lining the glandular acini become flattened, and many degenerate and disappear, so that eventually on microscopic examination few glands are seen, and such as remain are small and inactive. The stroma may contain granulation tissue, lymphocytes and plasma cells, but often there is merely fibrous tissue and no other evidence of inflammation.

It has been suggested that often the atrophic type of endometritis is not a bacterial disease but an atrophic process resulting from excessive or abnormal post-climacteric involution. It is a disease of great importance clinically, for it gives rise to the discharge of blood-stained purulent secretion, and may thus be mistaken for a carcinoma of the uterus.

CHRONIC METRITIS (Fibrosis Uteri)

This condition generally shows itself after the age of forty years, and in 90% to 95% of cases it affects parous women. It is essentially an affection of the fibro-muscular wall of the uterus, and the endometrium, though sometimes involved, is not necessarily so.

The uterus is enlarged symmetrically, and the consistence of both the body and the neck is firmer than normal. The enlargement is due to the thickness of the wall, which may increase from the normal average of 10 to 15 mm. to 25 mm. or more. In some cases the increased thickness is due to the presence of an excess of fibrous and elastic tissue, but usually in addition to this there is distinct hypertrophy of the muscle fibres. When the uterus is cut across with a knife it is seen that the wall is denser and harder than in health. It is little more vascular than normal and may be somewhat pale in colour, but the blood vessels are noticeably prominent on the cut surface, and their lumina tend to gape.

The microscopic appearance differs somewhat in parous and nulliparous women. In either there is extensive muscular hypertrophy and fibrosis, one or other feature often predominating, but in parous women there is also a striking increase of elastic tissue both in and around the blood vessel walls and between the muscle bundles. In either parous or nulliparous women the endometrium sometimes presents the appearance of chronic hypertrophic endometritis.

The cardinal sign of chronic metritis is hæmorrhage, which may be severe and uncontrollable. It is believed generally that the hæmorrhage results from the great proliferation of fibrous and elastic tissue, which prevents the contraction of the blood vessels and the retraction of their bleeding ends, but the alternative view has been proposed that the hæmorrhage is due to associated ovarian dysfunction, of which there is often evidence in the presence of fibrosis and multiple cysts.

The nature of chronic metritis is not clearly understood. In parous women it is usually regarded as a late result of mild puerperal infection or of "subinvolution." Normally in puerperal involution the large uterine arteries are replaced by smaller ones, which penetrate and canalize the organizing blood clot. The wall of the older vessels become fibrous and gradually disappear. It has been suggested that one of the chief factors in chronic metritis is the failure of absorption of the old vessel walls, and particularly of their elastic tissue. The muscular hypertrophy has been regarded as a compensatory process, an attempt on the part of the uterus to control and constrict its bleeding vessels. This cannot account for the process in nullipara, in whom there is no elastic and little fibrous tissue formation. It has been thought that in nulliparæ the primary lesion is endometrial, and that the muscular hypertrophy results from physiological efforts to expel the thickened endometrium.

FIBROMYOMA OF THE UTERUS (Fibroid Tumour)

The uterine fibromyoma is the commonest of all tumours. It is a simple encapsuled growth, derived from the fibromuscular tissue of the

uterine wall, and it is composed of unstriated muscle bundles and fibrous tissue in various proportions. In small tumours muscle predominates, but increased size and diminished vascularity lead to the development of much fibrous tissue between the bundles. The tumours are generally multiple and numerous, and the uterus may be studded in all parts with nodules of various sizes. In other cases the tumours are few in number, and one or more of them may reach large size. Occasionally there is a single tumour.

Uterine fibromyoma almost invariably originates during the reproductive period of life, particularly the latter part of that period. It is

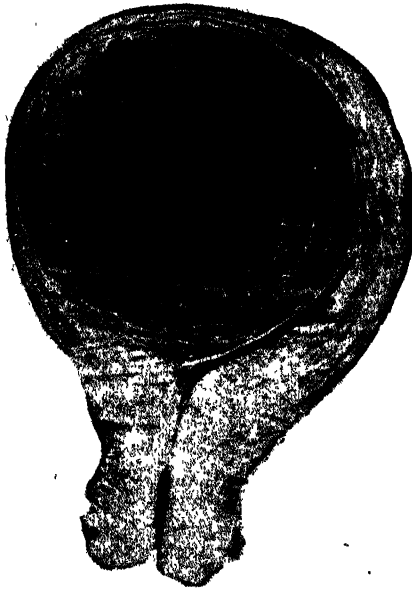


FIG. 288. Interstitial fibromyoma of the uterus. The tumour has undergone red degeneration.

(Department of Midwifery and Gynaecology, University of Edinburgh.)



FIG. 289. Submucous fibromyoma of the uterus. The uterus is distended with blood (hæmato-metra).

(Department of Midwifery and Gynaecology, University of Edinburgh.)

commonest in childless women, probably because its effects upon the form and vascularity of the uterus prevent implantation of the fertilized ovum.

Structure. A uterine fibromyoma is smooth and rounded, and completely encapsuled in condensed fibrous tissue. Except when degenerative changes have occurred, it is of hard consistency and when cut across imparts a creaking sensation to the knife. The cut surface of such a tumour is pale and glistening. The muscle bundles stand out prominently, and their whorled arrangement gives a characteristic appearance as of small tightly packed balls of wool. The periphery of the tumour has usually a plentiful blood supply, but in contrast to this the central portion is often ischæmic. Central degeneration often occurs, and this part of the tumour may be soft and cystic or fibrous or calcified.

Microscopically, the tumour is composed of intertwining bundles of plain muscle fibres separated by various amounts of fibrous tissue. The muscle bundles run in all directions, and in sections some are cut longitudinally, some transversely, some obliquely. The muscle and fibrous tissues are most easily distinguished by van Gieson's stain, for the muscle fibres take up the yellow picric acid and the fibrous tissue takes up the pink colour of fuchsin. Apart from their irregular arrangement, the muscle cells resemble those of the normal uterus except that the nuclei are somewhat shorter and more ovoid.

Varieties of Fibromyoma. The tumour at first lies within the muscular wall of the uterus, but from increase in size and from repeated contraction of the surrounding muscle it tends to project in various directions on either the inner or the outer aspect of the uterus.

All are at first *interstitial*, and some remain in this position. Interstitial tumours are commonly multiple and of small or moderate size, but occasionally they are solitary and large. They occur with equal frequency in all parts of the body of the uterus, and occasionally they affect the cervix. Interstitial tumours cause some enlargement of the uterus, often fairly symmetrical. Often they give rise to no symptoms, or they may cause hæmorrhage and dysmenorrhœa.

Subperitoneal fibromyoma is almost always multiple. It varies greatly in size, and one or more may attain large dimensions. At first they are sessile, but, with increase in size, they tend to become pedunculated, and eventually may swing freely from a narrow pedicle. The surface of such a tumour is often well supplied with blood vessels, which are evident as dilated channels coursing over it, but the centre is ischæmic. Consequently subperitoneal tumours are usually hard and often calcified, and they are very liable to degenerative changes. Torsion of such a tumour is also apt to occur, especially when the pedicle is long and narrow. Occasionally a large tumour with a short pedicle may involve the whole uterus in its torsion, with serious disturbance of the uterine circulation. Torsion of a fibromyoma leads to various forms of degenerative change and predisposes to infection. Sometimes the tumour becomes adherent to the omentum and viscera, and occasionally such adhesions may be sufficient to maintain the nutrition of the tumour after severance of its uterine attachment (the so-called parasitic myoma).

Submucous fibromyoma is less common than the subperitoneal variety and is less numerous and may be solitary. As a rule it is small and rounded or ovoid. It is extruded directly under the endometrium, and as a result of uterine contraction it becomes pedunculated, and may eventually project at the external orifice of the uterus. Impairment of the blood supply leads to necrosis, infection, and ulceration, often with profuse hæmorrhage.

Cervical fibromyoma accounts for less than 5% of all such tumours, a fortunate circumstance, for they sometimes have grave effects. A cervical tumour causes great elongation of the cervical canal, displaces the body of the uterus upwards, and projects forwards towards the bladder, backwards towards the rectum, or laterally into the broad

ligaments. In any of these situations it may cause pressure and give rise to grave complications during parturition.

Degenerative Changes in Fibromyoma. Owing to the paucity of its blood supply, a uterine fibromyoma is very liable to degenerative changes, especially in the central parts of the tumour, where the vascularity is least adequate. Degenerative changes may occur at any time, but they are most common during pregnancy or at the menopause. Sometimes volvulus of a pedunculated tumour determines the onset.

Mucoid or hyaline degeneration is the commonest type. It affects the cells of both the muscular and the fibrous elements of the tumour. The cells lose their definition, the fibrillar structure is lost, and a glassy hyaline material makes its appearance. As a result of the degeneration cystic spaces often develop, with rough, irregular walls and yellow, honey-coloured fluid content. Sometimes the cysts coalesce, and occasionally the greater part of the tumour becomes cystic.

Red degeneration, or necrobiosis, is a curious type of degeneration believed to result from fairly rapid interruption of the blood supply of a vascular tumour. There is much evidence to suggest that it is due to thrombosis or infarction, and that the peculiar changes are due to fatty degeneration with the liberation of hæmolytic lipid substances. The condition is common during pregnancy, since a fibromyoma is then unduly vascular, but it may occur at any time.

The central part of the tumour is affected first and to the greatest extent. It becomes softened, and in places almost of fluid consistency. On section it is seen to be of deep red colour, like raw meat, and it exhales a sickly odour. The red colour is due to hæmoglobin, which is liberated by rapid hæmolysis of extravasated blood cells. Microscopically there is extensive necrosis of the cellular elements, and nuclei are absent or faintly stained. In later stages, parts of the tumour liquefy, and irregular cystic spaces appear, containing structureless *débris* and brownish fluid. Much of the affected tissue does not become completely necrotic, and may survive and regenerate, hence the less preferable name, necrobiosis.

Fatty degeneration is very often visible microscopically, either alone or with other degenerative changes, but it is rarely met with to a degree appreciable to the naked eye.

Calcification occurs most often in the avascular, subserous tumours, especially in elderly women. The calcium deposits may be scattered diffusely through the tumour, or may form a thin irregular shell close under the surface. Sometimes the whole tumour may become calcified (the so-called womb-stone), and rarely such a tumour may loosen from its attachment and come to lie free in the peritoneal cavity.

Infection is most common in sloughing submucous fibroids. In subserous fibroids it is apt to occur after torsion of the pedicle, the organisms presumably being blood borne. Rarely infection by blood-borne organisms may arise as a sequel to necrobiosis.

Malignant Change in Fibromyoma. It has been said that 1% of fibromyomata eventually become sarcomatous, but general experience suggests that this is an unduly high estimate of its frequency, and many

authorities agree that the malignant change is extremely rare. Sarcomatous change has been observed most commonly in small areas in otherwise simple growths, and in these cases the diagnosis has been made upon microscopical examination after removal.

ENDOMETRIOMA : ADENOMYOMA

An endometrioma, or adenomyoma, is a simple tumour composed of glandular tissue and stroma resembling the uterine mucosa, sometimes incorporated in masses of plain muscle tissue. Such tumours are observed most often in the uterus, but they may arise in the ovary or in other parts of the pelvis, lower abdomen or abdominal wall.

An endometrioma occurs only in females, and it arises always during the reproductive period, especially after the thirtieth year. It is remarkable in possessing a functional activity which corresponds closely to that of the normal endometrium. It undergoes the same cycle of changes, and at the menstrual periods it proliferates, becomes congested, and discharges blood-stained fluid. Rarely it may even become the seat of decidua-formation. Its pathological features differ somewhat according to their origin.

A uterine endometrioma resembles an ordinary fibromyoma very closely, and in some cases the distinction can be made only by microscopic examination. The tumour arises most often in the upper part of the body of the uterus, especially on its posterior aspect near the cornu, and it does not affect the cervix. In some cases it is more or less circumscribed, but usually it takes the form of a diffuse thickening of the uterine wall. When cut across, it presents a dull grey or pink appearance, and may be cystic. Under the microscope it is seen to contain tubules or cysts lined by columnar epithelial cells surrounded by a stroma like that of the normal endometrium, the whole embedded in fibrous tissue and a variable amount of plain muscle.

An extra-uterine endometrioma is situated most often in relation to the ovaries or in the uterine tubes or the recto-vaginal septum. Occasionally it arises on the intestines, at the umbilicus, in laparotomy scars, or in the round ligaments of the uterus. In any of these situations



FIG. 290. Endometrioma of uterus. Acini lined by columnar cells are set in a stroma of fibrous tissue and plain muscle.

(Department of Pathology, University of Glasgow.)

it is a small tumour composed of glands and stroma of endometrial type, often with cysts.

An *ovarian endometrioma* is usually represented by cysts of hæmorrhagic character, often known as tarry or chocolate cysts. Often both ovaries are affected. The cysts are thick walled and usually are densely adherent to surrounding structures. They may rupture into the peritoneal cavity or may form localized fluid collections in the pelvis (see p. 703). *Endometrioma in the recto-vaginal septum* varies in size and may attain the dimension of the foetal head. Usually it is adherent to the vagina and rectum, and it may invade these organs. *Endometrioma of the intestines* is a small tumour, single or multiple, situated on the peritoneal aspect of the gut, especially on the pelvic colon. It appears as a roughening or granulation, and gives rise to dense adhesions. *Umbilical endometrioma* forms a small tumour which occupies the umbilical depression. At the menstrual period it enlarges visibly, assumes a red or purple colour, and becomes painful. It may become cystic or may open at the surface and discharge a blood-stained fluid. *Endometrioma in laparotomy scars* occurs generally after operations for ventral fixation of the uterus, and in appearance and behaviour it resembles the umbilical tumours. *Endometrioma of the round ligament* of the uterus forms a small rounded or oval mass situated either in the inguinal canal or in the groin or labium. It is generally ill-defined and adherent to neighbouring fasciæ, or it may be circumscribed and encapsuled. It may be mistaken for an omental hernia, and often a hernia is present.

Ætiology. Many theories have been advanced to account for endometrioma, and none is yet generally acceptable. It seems probable that the uterine and extra-uterine tumours differ in their modes of origin.

It is generally agreed that a uterine endometrioma is due to sequestration of endometrium in the wall of the uterus or in a fibromyoma, and that the isolated mucosa causes a reaction of the tissues around it so as to form a tumour. It is believed that the dislocation of endometrium is favoured by chronic endometritis.

The exact origin of extra-uterine endometrioma cannot be regarded as settled. At one time it was thought that the tumour was derived from remnants of the Wolffian body or of the Müllerian duct sequestered during development, but such a thesis is inapplicable to endometrioma in such situations as the abdominal wall.

At present there are two principal theories. The first, originally propounded by Iwanoff in 1898, and vigorously supported by Meyer, is based upon the fact that the endometrium, being formed from the Müllerian duct, is derived originally from the primitive coelomic epithelium and is thus closely allied embryologically to the lining cells of the peritoneal cavity. According to this serosa-epithelial theory, endometrioma arises from peritoneal cells that have undergone metaplasia, either as a result of inflammation or in response to excessive secretion of œstrin, the hormone that normally controls endometrial hyperplasia.

The second theory, to which most authorities now adhere, is the implantation theory put forward by Sampson. According to this view,

CARCINOMA OF THE UTERUS

endometrioma arises from adult endometrial cells that have been set free from their uterine bed and implanted in other sites. Harbitz has shown that endometrium transplanted experimentally in rabbits readily takes root in other tissues, and there responds to the influence of ovarian hormones and undergoes the same periodic changes as normal endometrium. It is thought that in some cases, notably in endometrioma in laparotomy scars, the cells are dislocated from the uterus as a result of the operation trauma. In others, the transference of endometrium is believed to be due to a process of retrograde menstruation, whereby endometrial fragments discharged during menstruation are carried along the uterine tubes and extruded into the peritoneal cavity.

CARCINOMA OF THE UTERUS

This is one of the commonest of all malignant tumours. In England and Wales it is responsible annually for the death of over 4,000 women, many in the prime of life. This mortality is only rivalled by that from cancer of the breast and cancer of the stomach.

Carcinoma may arise in the neck or in the body of the uterus, and in these situations it differs greatly in its incidence, progress and effects. Carcinoma of the cervix uteri is common, affects women who have borne children, and progresses rapidly: cancer of the body of the uterus is less common, occurs at a somewhat later age, principally affects nulliparæ, and is less malignant.

Carcinoma of the Cervix Uteri

Over 90% of uterine cancers arise in the cervix. They arise most often during the age period from thirty-five to fifty years—the period of functional senescence of the uterus—but are not uncommon a decade earlier. It is a striking fact that fully 96% of cases occur in women who have borne children, and there can be little doubt that this incidence depends upon the liability of the cervix uteri to laceration or other damage during childbirth. It is generally stated that women of more than average fertility are especially liable, but Deelman and others have shown that when their relative preponderance in the general population is taken into account multiparæ are little more subject to the disease than uniparæ. The trauma of the first labour is the determining factor. It is interesting to note that cancer of the neck of the uterus is rare in Jewesses.

The tumour may arise from the squamous epithelium covering the outer aspect of the cervix, or from the columnar cells of the endometrium lining the cervical canal or its glands. In some cases there is evidence that a cervical erosion provides the starting point.

All tumours of the cervix ulcerate readily, and consequently one of the first signs of carcinoma is hæmorrhage, which is especially apt to occur after coitus. Infection commonly supervenes and results in a thin, sanious discharge, often irritating and extremely offensive. In the later stages there is grave toxæmia from septic absorption.



FIG. 201. Carcinoma of the cervix uteri. The tumour is of infiltrating type and has destroyed the greater part of the cervix and begun to invade the body of the uterus. The surface of the tumour is extensively ulcerated.

(Department of Midwifery and Gynaecology, University of Edinburgh.)

older women. It takes the form of a small indurated plaque, which may be limited to the vaginal aspect of the cervix. Ulceration occurs early, but the growth spreads slowly and is somewhat less malignant than the other forms.

Microscopical Appearances. In most cases the growth is a squamous-cell

Gross Varieties. Carcinoma of the uterine neck, like growths elsewhere, exhibit variations both in outward appearance and in behaviour. It is customary to recognize three principal forms which are variations from the average rather than distinct types.

(1) *The Infiltrating Variety.* This is the commonest and the most malignant form. It usually arises at the site of an erosion or laceration, and spreads both on the vaginal aspect and along the cervical canal. Less often it is entirely within the canal, and is then not obvious on vaginal examination. The growth tends to infiltrate surrounding tissues, but does not project into the lumen to any great extent. Usually it ulcerates early.

(2) *The Proliferative Variety.* This is less common and is generally believed to be less malignant. It grows principally towards the lumen and forms a large, soft, fungating mass, which is very prone to bleed. In rare cases it may attain such size as to fill the whole vagina.

(3) *The Atrophic Variety.* This is the rarest form, and is chiefly met with in



FIG. 202. Carcinoma of the cervix uteri. $\times 90$. The tumour is of basal-cell type, and is composed of solid alveoli of spheroidal cells, which have infiltrated the uterine muscle.

(Laboratory of Royal College of Physicians of Edinburgh.)

carcinoma, but it differs in several respects from tumours of this class arising in the skin. It is composed of broad solid masses and branching columns of epithelial cells, but except in rare cases there are no cell nests, and prickle cells are usually absent. On casual inspection the tumour may be taken for a basal-cell carcinoma, but the cells usually show clear evidence of malignancy as indicated by mitotic figures and aberrations of form and nuclear character.

Degenerative changes in the centres of the epithelial masses lead to irregular spaces which may simulate glandular acini, and further confusion may be caused by the almost invariable presence of inflammatory change due to septic infection.

In a small proportion of cases the growth is a columnar cell adenocarcinoma, and sometimes glandular and squamous elements coexist.

Extension of the Tumour. Cancer of the cervix uteri has little tendency to disseminate and its gravity depends upon the tendency to local spread. The malignant cells soon invade the muscular coat, whence it is an easy step to the lymph vessels of the parametrium. Later the bladder, rectum, ureters and the peritoneum may be involved. The body of the uterus is sometimes invaded, but usually to a remarkably small extent.

Lymph glands may be involved early or late. The principal lymph channels follow the uterine artery.

Some of them terminate in small glands at the base of the broad ligament, while others pass directly to glands along the iliac vessels and in front of the sacrum. Often glandular enlargement found at operation is of inflammatory origin, due to superadded septic infection.

Extension of the disease beyond the uterus may cause distressing complications in the later stages. Involvement of pelvic nerves gives rise to severe pain. Invasion of bladder, ureters and rectum may lead to fistulae between these channels and the vagina. More frequently, pressure upon the ureters leads to hydronephrosis and suppurative nephritis, and eventually causes suppression of urine. Chronic uræmia is one of the most frequent causes of death.

Cancer of the Body of the Uterus

Less than 10% of uterine cancers affect the corpus uteri, and growths in this situation differ from those at the cervix in both incidence and behaviour. Nulliparae are far more liable to corporeal than to cervical cancer, and are affected in a considerable proportion



FIG. 293. Adenocarcinoma of the body of the uterus.
(Department of Midwifery and Gynaecology, University of Edinburgh.)

of cases. The age incidence is somewhat later and the disease is rarely seen before the menopause. This feature aids early recognition, for the cardinal sign, hæmorrhage, is more likely to attract notice after the menopause than at an earlier age. Cancer of the body of the uterus frequently occurs where the organ is the seat of fibromyoma, and it is sometimes held that there is a relation between the two conditions.



FIG. 294. Adenocarcinoma of the corpus uteri. $\times 275$. The tumour is composed of columnar cells arranged in irregular acini.

(Laboratory of Royal College of Physicians of Edinburgh.)

The tumour arises in the endometrium, and forms a mass of soft consistence which projects towards the uterine cavity. Several varieties are described, according as the tumour is bulky or ulcerating. The ulcerated form is the less common. Sometimes there are multiple nodules of carcinoma, which project in polypoidal fashion from different parts of the wall. Occasionally the whole endometrium is affected diffusely.

Microscopically, the growth is an adenocarcinoma. It is composed of columnar cells, which for the most part are arranged in acini. Sometimes the acini are few and the cells lie in solid masses—the so-called carcinoma simplex. The acini are usually irregular in size and shape, but sometimes they can hardly be distinguished from the glandular spaces of normal endometrium. In such cases the diagnosis is made upon evidence of invasion of the growing edge, and upon changes in cell form and nuclear structure.

The progress of cancer of the body of the uterus is slow, and thus the prognosis after operative removal is more hopeful than in cancer of the cervix. For a long time the disease may be limited to the uterus itself. Eventually the parametrium is reached, and neighbouring viscera may then be affected. The lymph glands are involved at a late stage.

SARCOMA OF THE UTERUS

Sarcoma of the uterus is an uncommon form of growth. It may occur at any time of life, even in infancy, and, unlike carcinoma, it is considerably more apt to involve the body than the cervix.

Sarcoma may arise in the fibromuscular wall of the uterus or in the endometrium. Often it is impossible to determine the exact

origin, but there is no practical disadvantage in this, for the tumours do not differ in any important particular.

It is generally stated that sarcoma commonly arises in fibromyoma of the uterus, but it seems probable that this view is inaccurate and that sarcomatous change in a fibromyoma is exceedingly rare. Sometimes the origin of the tumour may be traced to the plain muscle fibres of the uterus, and the growth may then be regarded as a myo-sarcoma. Rarely striped muscle fibres are present, and the tumour must then be looked upon as a mixed mesoblastic tumour.

Whether derived from the fibromuscular wall or the endometrium, a uterine sarcoma may be circumscribed or diffuse.

Circumscribed Sarcoma. A circumscribed sarcoma forms a soft tumour, which grows rapidly and may attain considerable size. The cut surface is usually brain-like, of greyish colour, but interrupted in places by areas of necrosis and hæmorrhage, or by irregular cyst-like cavities containing *débris* and blood clot. Microscopically, there are round and spindle-shaped cells, and sometimes multinucleated giant cells.

Diffuse Sarcoma. A diffuse sarcoma usually appears to originate in the endometrium, and it may spread over the greater part or the whole of the inner aspect of the uterus. In such a case the uterus is uniformly enlarged, and resembles the pregnant uterus. The endometrium is greatly thickened, and its surface shaggy and ulcerated or covered by nodular or polypoidal outgrowths. In some cases the line of separation between the endometrium and the fibromuscular wall is distinct, but often both layers are diffusely infiltrated by the tumour. Microscopically, spindle cells and round cells are present. Blood vessels are numerous, large and thin walled. The epithelial elements of the endometrium are usually destroyed, but occasionally a few of the endometrial glands persist and are recognizable.

Two special varieties of uterine sarcoma deserve further mention :—

(1) **Recurring Polypi.** In a certain proportion of cases recurrence takes place after curettage of submucous uterine polypi, and eventually, after repeated recurrence, true malignant invasive properties may develop. In some such cases no doubt the tumour is a submucous fibromyoma that has undergone sarcomatous change. In others the tumour is probably of low-grade malignancy from the beginning.

(2) **Grape-like Sarcoma (Sarcoma Botryoides).** This tumour may occur in infancy, childhood or adult life. It arises in the cervix and projects towards the vagina, where it forms a lobulated mass somewhat resembling a bunch of grapes. Sometimes the tumour attains great size, and it may fill and distend the whole vagina. The tumour is composed of round or spindle-shaped cells set in a very œdematous matrix which explains its soft, cyst-like character.

TUMOURS OF THE CHORION

The chorion, the outer covering membrane of the embryo, is endowed with the property of invading the uterine wall. In virtue of this property it ensures the proper implantation of the ovum and its subsequent

nutrition from the maternal blood stream. In normal circumstances this great capacity for proliferation and invasion is restrained, and only proceeds to the extent required by the needs of the embryo; and at the end of pregnancy the whole zone of invasion is cast off in the placenta. In rare cases, however, and in circumstances at present unknown, the invasion of the chorion proceeds unrestrained, and a tumour results.

It is necessary to consider first the normal structure of the part. The chorion is an embryonic tissue and consists of a stroma of meso-

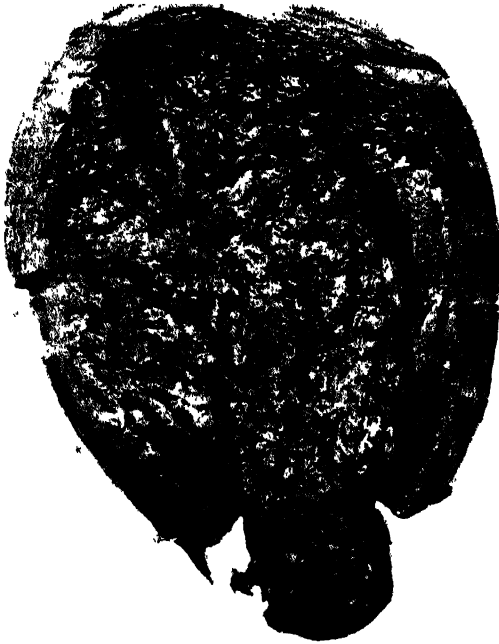


FIG. 295. Enlarged uterus containing hydatidiform mole. As a consequence of fixation in formalin, many of the grape-like polypi have shrunk.

(Department of Midwifery and Gynaecology, University of Edinburgh.)

blastic origin and a covering layer, the trophoblast, derived from ectoderm. The trophoblast is made up of two layers, an inner layer of a single row of *Langhans* cells—large, well-defined, cuboidal cells with dark nuclei and clear cytoplasm—and an outer layer, the syncytium, which is composed of dense protoplasmic masses containing many nuclei.

At an early stage in its development the chorion is raised into innumerable villi, each of which consists of a mesenchymal core containing primitive blood vessels and surmounted by the two layers of the trophoblast. The outer layer, the syncytium, destroys the surrounding maternal endometrium and erodes its vessels, so that the

maternal blood flows into irregular spaces around the villi and comes into close relation with the foetal blood inside the villi.

Chorionic tumours retain this propensity for eroding maternal blood vessels, and, as a result, they tend to bleed profusely and also to disseminate early by the blood stream. Even apart from tumours, fragments of the chorion are sometimes set free in the blood stream. According to Sëhmorl, such déportation of small chorionic emboli occurs in almost 80% of normal pregnancies, and in a few cases on reaching the lungs these emboli may assume active growth.

Tumours of the chorion vary greatly in appearance and behaviour, and there is a continuous range from the simple to the excessively malignant. The most simple type is the *hydatidiform* or *vesicular mole*. This is sometimes regarded as a degeneration product of the placenta, but there seems little doubt that the degenerative changes have an underlying neoplastic basis. Next in the series is the *invasive mole*, or *chorioadenoma* (Ewing). This is sometimes classed as a form of hydatid mole, but it differs essentially from this in the extent of invasion of the uterine wall, and, as Novak has pointed out, it is better regarded as a carcinoma of low malignancy. Lastly, there is the *choriocarcinoma* (*chorion-epithelioma*), a growth of intensely malignant character.

All the tumours of this class differ in one important respect from most other neoplasms, namely, that they are not derived from the host but from another individual, the embryo. They are parasitic growths, and in this respect they are comparable to certain kinds of teratoma.

Hydatidiform Mole (*Vesicular* or *Placental Mole*). This condition is generally regarded as a degenerative change affecting the chorion, but there is evidence to suggest that in some cases at least it is more correctly looked upon as a form of abnormal proliferation bordering on neoplasia. It is a rare condition, and is said to occur only once in every two or three thousand pregnancies. Multiparæ are affected more often than primigravidæ, and sometimes the disease reappears at subsequent pregnancies. The mole starts in the early months of

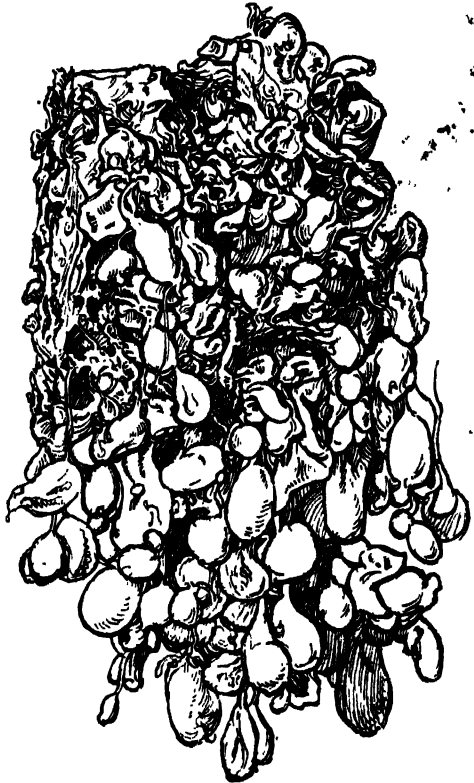


FIG. 296. Hydatidiform mole.

(Museum of Royal College of Surgeons of Edinburgh.)

pregnancy, and is rare after the fourth month. When it occurs early and affects the whole placenta the embryo disappears and no traces of it can be found. When the mole occurs later, or when it affects only a part of the placenta, the embryo may survive for a short time, but sooner or later abortion occurs. The mole is usually cast off at the time of abortion, but a part of it may remain in the uterus and continue to grow.

The mole is composed of clusters of small, tense lobules, which are often likened to white currants or small grapes. Sometimes it may attain a weight of two or three pounds. Hæmorrhage occurs readily, and often the mole is partially buried in clots of blood.

Microscopic examination shows that the grape-like structures are



FIG. 297. Hydatidiform mole. $\times 90$. The villi, which are seen in cross-section, have a characteristic bladder-like appearance, due to mucoid degeneration of the supporting stroma.

(Laboratory of Royal College of Physicians of Edinburgh.)

distended, hyperplastic villi of the chorion (see Fig. 297). The central core of each is composed of myxomatous tissue in a state of extreme œdema, and to this the tense, shining appearance of the lobules is due. The two layers of the trophoblast are present on the surface, and often show signs of active proliferation.

Invasive Mole (*Choriadenoma Destruens*). This is apt to follow a simple hydatidiform mole, either within a short time of its discharge or after a period of several months. It forms a bulky tumour which fills the uterus and burrows into its wall. Sometimes the uterine wall is honeycombed by tumour tissue and areas of hæmorrhage, and occasionally the tumour penetrates as far as the peritoneum. It may then cause death by hæmorrhage into the peritoneal cavity.

The microscopic appearance is characteristic. The tumour differs from choriocarcinoma in containing all the elements of the chorion,

both the mesenchymal core and the epithelial trophoblast. The connective tissue is cellular, and may be swollen by œdema. The *Langhans* cells are increased in number, and instead of forming a single row they lie in broad sheets of irregular shape. The syncytial buds are large and abundant.

In most cases the growth remains limited to the uterus, but occasionally it metastasizes either in the pelvic tissues or in the

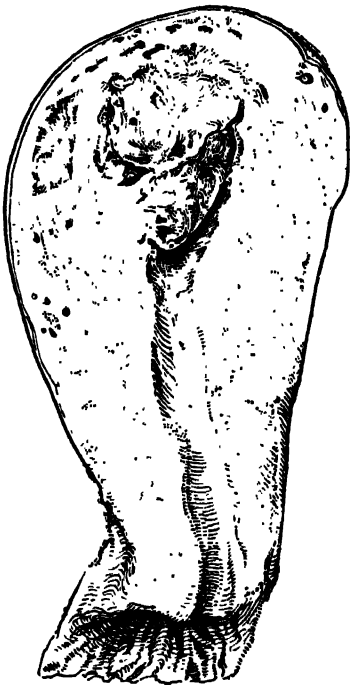


FIG. 298. Choriocarcinoma of the uterus. The tumour is situated at the fundus of the uterus. A part of it projects into the uterine cavity, while the major part infiltrates the wall adjacent.

(Museum of Royal College of Surgeons of Edinburgh.)



FIG. 299. Choriocarcinoma. $\times 275$. The tumour is composed of confused masses of chorionic epithelium. The middle part of the figure is occupied by syncytial masses, while above and below there are collections of *Langhans* cells.

(Laboratory of Royal College of Physicians of Edinburgh.)

lungs. Rarely metastases have been found in the vagina, projecting from the wall as small circumscribed tumours of bluish colour.

Choriocarcinoma (*Chorion-epithelioma*). This is the most actively progressive form of chorionic tumour, and is one of the most malignant of all tumours. It is composed of the cells of the trophoblast alone, and the mesenchyme of the chorionic villi takes no part in its formation. Usually the tumour develops in retained portions of a hydatidiform mole, but it may occur in an otherwise normal pregnancy or puerperium. Occasionally it has been observed several years after childbirth or abortion. In the great majority of cases it arises in the uterus, but occasionally in the vagina, uterine tube, or ovary. Tumours of the

structure of choriocarcinoma have occasionally been observed in other situations, for instance in the testis. Such tumours are to be regarded as teratomata, with a preponderance of ectodermal structures.

In the uterus the tumour commonly arises at the placental site, near the fundus. The principal mass of the tumour lies in the muscular wall and projects on the inner aspect of the uterus. Sometimes it extends to the peritoneal surface. It forms a soft friable mass, and owing to hæmorrhage it is of claret or maroon colour. The surface is ulcerated, and bleeds freely.

Microscopically, there are islets of actively growing cells of the *Langhans* type, mingled with irregular masses and strands of syncytium. Blood vessels are particularly susceptible to the invasive properties of the syncytium and therefore large extravasations of blood surround and infiltrate the growth. The uterine wall is extensively invaded, and tumour cells may sometimes be seen lying in the lumen of the blood sinuses. The growth possesses no stroma, and has no blood vessels of its own. It derives its whole nourishment from extravasated blood.

Choriocarcinoma progresses rapidly, and unless hysterectomy is performed death usually takes place within from six to eighteen months. The growth disseminates by the blood stream, especially to the lungs. Sometimes secondary growths appear in the vaginal wall and elsewhere in the pelvis. It is often stated that metastases may disappear spontaneously after removal of the primary growth, but according to Ewing such behaviour is rare in true choriocarcinoma though not uncommon in syncytioma.

Syncytioma. In 1895, Marchand, who was the first to demonstrate the chorionic origin of chorion-epithelioma, distinguished two forms, the typical form (which corresponds to the description of choriocarcinoma above), and the uncommon atypical form. The latter is now generally known as a syncytioma. It is a bulky tumour which infiltrates the uterine wall, but it differs from the "typical" form in its great tendency to undergo retrogression. It is composed of large giant cells with the general characters of chorionic syncytium. These are scattered diffusely and mingled with masses of fibrin and necrotic debris, in which are numerous wandering and inflammatory cells. The condition is sometimes regarded as a distinct tumour with a definite tendency to retrogression, but according to Ewing it is merely a degenerative form of one of the less malignant types of chorionic tumour.

Ovarian Changes with Chorionic Tumours. Marchand drew attention to the frequent association of ovarian cysts with chorionic tumours, an observation which has been amply confirmed by subsequent experience. The cysts are of lutein type and may affect both ovaries and be so large that they are palpable above the pubes. Their cause is not known. The hormone *lutein* is believed to control implantation of the ovum, and it may also control growth of the chorion, but there is no evidence that abnormal lutein production predisposes to the growth of the tumour. It is known that the corpus luteum itself is controlled by other secretions, possibly of placental origin, and the ovarian cysts are

probably due to excessive production of this secretion. This would explain the disappearance of the cysts which sometimes follows successful removal of the tumour.

SALPINGITIS

Salpingitis results usually from an ascending infection from the uterus and vagina, less commonly from a contact infection from adjacent structures, such as the appendix, and rarely, apart from tuberculous salpingitis, from hæmatogenous infection. The majority of cases of acute salpingitis are of gonorrhœal origin.

Chronic salpingitis, excluding tuberculous disease, is almost always a sequel to an acute or subacute attack. In virtue of the innumerable folds and crevices in its mucous membrane, the tube forms an ideal site for the maintenance of infection, especially by organisms of low-grade virulence, such as gonococci. Chronic gonococcal salpingitis is therefore common.

Gonococcal salpingitis may have an acute onset, with severe local and general effects, but rather more frequently the onset is subacute and of mild type.

The disease may arise a short time after the primary infection, or after a long interval. If delayed it may depend upon some exacerbation of the disease in the urethra or cervix, or it may represent a recrudescence of an earlier mild infection of the tube. Usually both tubes are affected.

The mucous membrane is principally involved, and its many folds become congested and greatly swollen by oedema. At an early stage the fimbriæ are swollen and turgid, and from the abdominal ostium a few drops of yellow pus may be expressed. At this stage there is commonly a mild degree of peritonitis, principally limited to the pelvis. The pelvic peritoneal surfaces are congested and lose their normal sheen, and the cavity contains a small quantity of sero-purulent exudate. In some cases the peritonitis is more extensive. The whole lower abdomen may be affected, and the coils of ileum may be glued together by lymph exudate. A purulent collection may form in the pelvis.

The acute phase almost invariably subsides in the course of a short time, but complete resolution often does not occur. There is a very great tendency to the formation of adhesions, either delicate filmy membranes, or tough bands of fibrous tissue.

In chronic salpingitis the tubes are fibrous and thick walled, and are often buried with the ovaries, uterus, bladder and broad ligaments in a solid fibrous mass, and the pelvic colon and pelvic coils of ileum also may be involved. In some cases, when the tubes are thickened and fleshy, numerous nodules may develop in the tubal wall and project both into the lumen and under the serous surface. Such a nodular thickening develops most frequently at the isthmus of the tube, *i.e.*, where the tube joins the uterine cornu (*salpingitis isthmica nodosa*). Microscopically, the nodules are seen to contain numerous gland-like acini, are lined by mucous membrane, surrounded by hypertrophied bundles of muscle and fibrous tissue. It is presumed that in such cases

portions of the mucous membrane have been forced by intra-tubal pressure into the muscle wall of the tube, and that the epithelium of the diverticula thus produced has proliferated as a response to the presence of a chronic infection.

Sometimes the lumen of the tube remains patent, but usually its two orifices become occluded, and it may then distend with watery fluid or with pus (hydrosalpinx and pyosalpinx).

Hydrosalpinx occurs when the infection is of a mild degree of virulence. The tube is dilated by watery fluid derived from its lining cells, and eventually it may attain considerable size and fill the greater part of the pelvis. The fimbriated orifice is occluded, partly by annular fibrosis, and partly by retraction of the fimbriæ into the tube; and after the occlusion is so complete that the site of the orifice cannot be distinguished. The lateral end of the tube dilates to the greatest extent, and as dilatation is restrained by the peritoneal covering it gradually assumes a characteristic retort shape. The walls are sometimes thin and translucent and are readily torn.

Pyosalpinx results when the infection is somewhat more severe. The uterine ostium is occluded by œdema, and the abdominal ostium is closed either by indrawing of the fimbriæ or by a kind of sucker action, whereby the fimbriæ adhere to adjacent structures. The tube becomes distended, but usually not to the same degree as in hydrosalpinx, for its walls are inflamed, thickened, and infiltrated with polymorphs, lymphocytes and plasma cells. Sometimes, especially in tuberculous infections, a pyosalpinx may attain great size. Often the surrounding tissues and coils of intestine are adherent. Not infrequently the abscess is not limited to the tube itself, but lies in a cavity walled in by adhesions between tubes, broad ligament and ovary, a *tubo-ovarian abscess*. The ovary itself may be infected, especially if a large Graafian follicle is present, and sometimes it is almost completely filled with pus.

Usually the pus is yellowish-white and odourless, but it may be of a dirty colour and foul smelling. Often, despite this appearance, cultures yield no growth, for the causative organisms, gonococci and their associated non-hæmolytic streptococci, tend to die out on prolonged sequestration. For this reason active surgical treatment is not usually required. In a few cases the abscess is infected secondarily by *Bacillus coli*, or other organisms.

Tuberculous Salpingitis. Tuberculous salpingitis is not uncommon, but since the gross appearance often differs little from non-tuberculous salpingitis its specific character is not always obvious. The disease is invariably secondary to tuberculosis in other parts of the body, and is generally attributed to hæmatogenous infection. It is usually bilateral.

Tubercles develop in the mucous and submucous coats, which become infiltrated with lymphocytes and endothelial cells. Tubercles may develop also under the subserous coat, and in this case the diagnosis on direct inspection is more easy. In many cases the tube is distended with caseous material so that it resembles a pyosalpinx. Adhesions surround the tube and bind it to adjacent viscera.

Tuberculous salpingitis is frequently associated with some degree of

tuberculous peritonitis. In some of these cases it is possible that the tube is infected from the peritoneum, but more frequently the peritoneal lesions are secondary to tuberculosis of the tube. The practical importance of this is that removal of the diseased tube may promote recovery from the peritonitis.

TUMOURS OF THE UTERINE TUBES

Tumours of the uterine tubes are rare. The least uncommon are malignant adenoma and carcinoma. Papilloma, sarcoma, fibroma, teratoma, lymphangioma, and other forms of growth have been described. Primary carcinoma occurs usually at about the period of the menopause and in 80% of cases the disease is bilateral. On inspection it may be mistaken for chronic salpingitis with pyosalpinx, which it somewhat resembles. The tube is enlarged and thick, and may contain watery fluid or pus. Much of the lumen is occupied by a friable cauliflower-like growth which may be cystic in places. Usually the tumour is an adenocarcinoma. It is generally supposed to arise from the mucous membrane of the tubes, but an origin from Wolffian remnants in the parovarium has been suggested. In some cases there is evidence that the tumour arises on a basis of old inflammatory disease in the tube.

The uterine tubes are often involved in secondary carcinoma derived from the uterus, ovary, rectum, colon or stomach.

CYSTS AND TUMOURS OF THE OVARY

The ovary is a common site for cysts and cystic tumours. These vary greatly in nature and appearance. Many are of simple type, and result from distension of a Graafian follicle or corpus luteum, others have the characters of simple neoplasms, while yet others exhibit malignant properties. Solid tumours also occur in the ovary, but are less common. The cysts in most cases conform to regular types, but a certain proportion are of a mixed or atypical character, and defy exact classification. The following are the principal types:—

Simple Cysts

- (1) Follicular and luteal.
- (2) Endometrial.
- (3) Blood.

Solid and Cystic Tumours

- (1) Multilocular or compound cystadenoma (pseudomucinous cyst).
- (2) Papilliferous cystadenoma (papillary or serous cyst).
- (3) Teratoma (dermoid cyst).
- (4) Granulosa-cell tumour.
- (5) Arrhenoblastoma.
- (6) Primary carcinoma.
- (7) Secondary carcinoma.
- (8) Connective-tissue tumours.

Follicular and Luteal Cysts

During the reproductive period of life a succession of changes occurs in the Graafian follicles, whereby they mature, discharge their ripe ova into the peritoneal cavity, and then develop into corpora lutea. It is certain that at least one ovum is set free during every menstrual cycle, and consequently the follicles which attain maturity between puberty and the menopause number several hundred. The normal ovary at birth, however, contains an immense number of immature follicles, probably in the neighbourhood of 30,000, and the vast majority of these gradually undergo atrophy or atresia. It is evident that in adult life the ovary will contain follicles in all stages of development, atresic follicles, immature and mature follicles, and corpora lutea, and any of these may undergo cystic change. It is generally believed that in adults the cysts arise principally in mature or almost mature follicles, but atresic follicles are also liable to cystic change. Cyst formation is usually attributed to chronic inflammation or congestion of the ovaries, but it must be admitted that there is not always evidence of this, and it seems likely that sometimes the origin is to be found in perversion of physiological processes in the follicle, rather than in any gross pathological factor.

Follicular cysts are most common during the reproductive period, but they may occur in childhood or even in infancy. They are rare after the menopause. The cysts are usually multiple and bilateral, and in some cases both ovaries are almost completely involved. The cysts are generally small, and rarely distend the ovary beyond the size of a golf ball.

The cysts are unilocular and contain watery fluid, which occasionally is coloured by old or recent blood. The walls are smooth and fibrous, and the smaller cysts are sometimes lined by a single layer of columnar or cubical epithelium. Often the cyst wall contains lutein cells similar to those of the corpus luteum, but differing from them in being derived from the theca interna and not from the membrana granulosa of the follicle.

Lutein cysts are much less common than follicular cysts. They are usually single and may attain the size of a walnut, or even of a hen's egg. A characteristic feature is the presence of a thick fibrous wall of wavy contour and bright yellow colour. The wall contains numerous luteal cells, large rounded cells containing quantities of cholesterol and other lipoids, to which the yellow colour is due. Sometimes a lining membrane of cubical cells is present. The content of the cyst may be clear watery fluid but it is often blood-stained.

Occasionally luteal cysts are multiple and bilateral (compound luteal cyst). These are usually related to pregnancy or to hydatid moles or choriocarcinoma. The cysts may attain the size of the fetal head. After parturition, or after removal of the mole or carcinoma, they may diminish in size (*see p. 698*).

Endometrial Cysts (Chocolate Cysts)

Endometrial cysts of the ovary are most common between the ages thirty and forty-five years, and they are unknown before puberty.

and rare after the menopause. They are small cysts, usually from 2 to 4 cm. in diameter, and often both ovaries are affected.

The cysts are due to hæmorrhage from ectopic endometrial tissue (*see p. 687*), and on microscopic examination such tissue may be seen in small areas of the cyst wall. The hæmorrhage occurs at the menstrual periods, for the ectopic endometrium undergoes the same cycle of functional activity as normal endometrium. The content of the cysts resembles menstrual blood. It remains fluid and acquires a tarry or chocolate colour.

An endometrial cyst, when small, lies under the surface of the ovary, but when distended by recurring bleeding it is very apt to perforate and to discharge its contents into the peritoneal cavity. The endometrial blood being irritant stimulates peritoneal adhesions, which generally are limited to the pelvis, but may sometimes implicate the



FIG. 300. Bilateral follicular ovarian cysts.
(*Department of Midwifery and Gynæcology, University of Edinburgh.*)

intestines. In some cases the effused blood is not absorbed, but forms a fluid collection in the pelvis and becomes circumscribed by adhesions which bind together the ovary and the posterior surface of the uterus. The adhesions may be very dense and hard, and the condition may simulate a tubo-ovarian abscess or a tumour. Continued activity of the aberrant endometrium may cause the fluid collection to increase in amount.

Blood Cysts : Hæmatomata

Hæmorrhage is most apt to occur in endometrial or in luteal cysts, but it is not infrequent in other types. In large cysts it is especially apt to arise when torsion or kinking of the pedicle leads to obstruction of the venous return. The ovary becomes tense with extravasated blood. The cyst may rupture, and a considerable amount of blood may then collect in the peritoneal cavity. In most cases, however, the blood clots and is ultimately absorbed. Occasionally infection of the clot leads to abscess formation.

Multilocular Cystadenoma (Pseudomucinous Cyst)

This is the commonest of all ovarian tumours. It is a true tumour and results from proliferation of epithelial cells, which are probably,

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derived from downgrowths from the germinal epithelium. The tumour undergoes cystic dilatation by the secretory products derived from its epithelial cells. As the tumour grows, its epithelium projects in various directions in a somewhat complicated manner, and in this way secondary loculi develop either inside the principal cyst or in the substance of its wall.

Pseudomucinous cysts are usually unilateral, but in a small proportion they are bilateral. If untreated, they sometimes attain great size, and in pre-operation days cysts of 50 lb. or even 100 lb. weight occurred. They rarely spread towards the broad ligament, and in the great majority of cases they become more and more pedunculated,



FIG. 301. Multilocular (pseudomucinous) cystadenoma of the ovary. A section of two portions of the cyst wall. $\times 275$. The lining membrane is composed of tall columnar cells containing large globules of pseudomucin.

(Laboratory of Royal College of Physicians of Edinburgh.)

and project upwards into the abdomen. The cysts are of rounded form and smooth surface, with undulations corresponding to the different loculi.

Microscopic examination shows that the cyst wall is composed of fibrous tissue lined by a layer of columnar epithelium. The epithelium consists of a single row of tall columnar cells, of remarkably uniform appearance. Each cell has a deeply placed nucleus and a peculiarly clear protoplasm. In places the epithelium is raised into papillary processes, but not so commonly as in the papillary type of cystadenoma.

The cysts contain glairy, mucoid material of aropy consistency. Sometimes it is quite clear and almost colourless, but often it is turbid from debris and cholesterol crystals, and it may resemble pus. Often it is tinged with altered blood pigment. The glairy material is pseudomucin, a substance that differs from mucin in its staining reactions and in the facility with which it may be precipitated by acetic acid.

The tumours usually follow a benign course, but there are intermediate forms which possess some of the characters of a papillary cyst-



FIG. 802. Bilateral papillary cystadenomata of the ovaries.

(Department of Midwifery and Gynaecology, University of Edinburgh.)

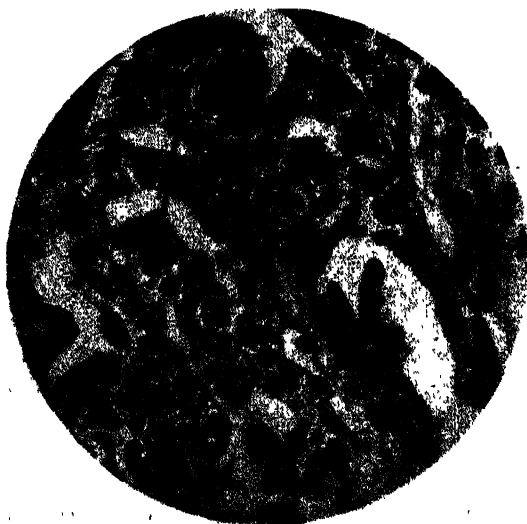


FIG. 803. Papillary cystadenoma of the ovary. $\times 275$. The tumour is composed of columnar epithelial cells arranged in a papillary formation upon fine branching cores of connective tissue. The malignant character is indicated by the complex structure, by the nuclear hyperchromatosis and by the presence of mitotic figures.

(Laboratory of Royal College of Physicians of Edinburgh.)

adenoma, and these occasionally exhibit malignant properties. Pedunculation favours the occurrence of volvulus of the cyst. Occasion-

ally a cyst ruptures and discharges mucoid material into the peritoneal cavity, leading to the condition of pseudomyxoma peritonei (*see* p. 544).

Papillary Cystadenoma

Papillary cysts are much less common than the pseudomucinous cyst, but they are by no means rare. They are characterized by more vigorous growth on the part of the epithelial cells, which project either into the cysts or on their outer aspect, in the form of multiple warty or papillomatous excrescences. Both ovaries are usually affected. In each ovary there is generally one principal cyst, sometimes with a number of small subsidiary ones in its wall.

The cyst attains moderate dimensions, and rarely grows to such great size as a multilocular cystadenoma. It differs also in the character of the content, which is of watery consistency and contains albumin but no pseudomucin.

The most characteristic feature is the presence of papillary processes. Usually these are limited to one portion, and project internally into the cyst, but sometimes they cover the whole wall, and may grow to such an extent as to fill the greater part of the cyst. Not infrequently similar papillary processes grow also from the outer aspect of the cyst, and project into the peritoneal cavity. This type is very apt to become malignant.

Microscopically, the cyst has a lining of low columnar or cubical epithelial cells, which are sometimes ciliated. The papillary processes, which are covered with epithelium of a similar type, vary greatly in form. Some are of simple structure, but others branch in complicated fashion and show evidence of proliferation.

Papillary cysts are on the borderline of malignancy, and the cancerous change develops in a considerable proportion, probably about 20%. Malignancy is especially apt to take place when papillary growths project from the outer surface, but such projections are not a necessary prelude to malignancy. Frequently the cells are disseminated into the peritoneal cavity, and set up metastases either in the pelvis or throughout the abdomen. Such dissemination may occur even when the cyst shows no gross evidence of malignancy. Remarkably enough, removal of the primary tumour may cause temporary retrogression or even disappearance of the metastases, though ultimately they almost always recur and prove fatal.

Teratoma (Dermoid Cyst)

Teratoma of the ovary is not uncommon, and is said to constitute about 10% of all ovarian tumours. It is generally described as a dermoid cyst, but as it contains tissues derived from all the three embryonic layers it is rightly regarded as a teratoma. It is a benign tumour, but in rare cases malignant change may supervene. The tumour grows slowly and rarely attains great size. In a small proportion of cases both ovaries are affected. The greater part of the tumour is cystic, and contains fatty sebaceous material and often masses of hair and epithelial debris. The cyst is lined by stratified squamous

epithelium in which hair follicles and sebaceous and sweat glands may be recognized. At one side of the cyst there is usually a raised plaque, and teeth may project from its surface. The wall deep to this plaque contains various tissues derived from mesoderm and entoderm. Cartilage, non-striped muscle and glandular acini preponderate, and bone, thyroid tissue and even nerve cells may be present. Occasionally tissue resembling the chorionic epithelium is found.

It is obvious that such a teratoma arises from totipotent cells, and there are two principal views in regard to its origin in the ovary. It has been suggested that it is derived from germ cells, ova, that have undergone a kind of parthenogenetic development, for it is known



FIG. 304. Teratoma (dermoid cyst) of the ovary. A quantity of hair is seen growing from the wall, and several teeth project inside the cyst.

(Department of Midwifery and Gynaecology, University of Edinburgh.)

that the ova of certain lower species may be stimulated to growth without fertilization by spermatocytes. But such a theory takes no account of the occurrence of similar teratoma in the testis, and there are other pertinent objections to its acceptance. The prevailing view is that the teratoma is derived from dislocated blastomeres, which are known, in lower vertebrates at least, to be capable of forming a complete embryo.

Granulosa-cell Tumour

This somewhat uncommon tumour occurs at any age, but especially in women who have passed the menopause. The tumour cells resemble the normal cells of the membrana granulosa of the Graafian follicle. The special interest of the tumour lies in the fact that it appears to produce an internal secretion which stimulates endometrial proliferation and leads to enlargement of the uterus and periodic hemorrhages.

The tumour is generally unilateral, and usually of benign type. In a small proportion of cases, however, it is malignant. Generally, it

is of moderate size, although there are examples recorded in which the tumour has attained the size of a man's head.

The tumour is encapsuled, with a thick fibrous sheath. It is partly solid, fleshy in appearance and somewhat vascular, partly occupied by cysts containing clear, straw-coloured fluid.

Microscopically, the solid parts of the tumour consist of densely packed masses of polygonal cells, uniform in size, shape and staining qualities. These cells, which sometimes show mitotic figures, resemble closely the cells of the granulosa layer of the Graafian follicle.

The cysts vary in appearance. The smaller ones are lined by a single layer of cuboid or flattened epithelial cells. The larger ones, on the other hand, show a characteristic structure somewhat resembling that of a normal follicle. The lining membrane consists of several layers of granulosa cells, closely packed polygonal cells with dark blue nuclei and scanty cytoplasm. The cells in the outermost part of this layer tend to be cuboidal in shape, and are supported on a basement membrane. In some cases outside the basement membrane there is a single row of clear or light-staining cells resembling the theca interna of the follicle.

The origin of these tumours is not clearly understood. It has been supposed that they arise from adult granulosa cells of a mature follicle. That they generally occur in elderly women, and that they are sometimes found in the medullary part of the ovary, where mature follicles do not occur, has led to the belief that they arise in embryonic rests present in the ovarian parenchyma.

Arrhenoblastoma

This rare tumour is interesting from the fact that it produces a hormone or group of hormones which alters the secondary sexual characters towards the masculine type. The tumour occurs at any age period between puberty and the menopause, grows rapidly and may attain very large size, especially if cystic. It may be simple or malignant. Microscopically, it consists mainly of undifferentiated small round or spindle cells, and may resemble a sarcoma. In some cases there are areas occupied by cells of epithelial appearance, arranged in cords or lining tubules somewhat resembling the testicular tubules.

One of the first results of the tumour is cessation of the menstrual periods. The condition may thus be mistaken for pregnancy, but may be distinguished by the fact that the Aschheim-Zondek test is negative. Later the breasts atrophy, the hair of the head falls out or its growth ceases, while there is an excessive development of hair on the lips and chin and on other parts of the body. The distribution of pubic hair assumes the masculine type, and hypertrophy of the clitoris may develop. Operative removal of the tumour leads to restoration of the feminine characters. In some cases recurrence of the tumour has been followed by reappearance of the classical syndrome.

The origin of the tumour, and the nature of its hormones, are not understood. It has been suggested that the tumour is derived from

primitive undifferentiated germ cells in the hilum of the ovary, and that these cells acquire characters similar to the cells of Leydig, the interstitial cells of the testis.

Primary Carcinoma of the Ovary

Primary carcinoma of the ovary is less common than secondary growths. It occurs in adults, frequently at a comparatively early period of life, and may affect nulliparæ or multiparæ. It usually arises in a pre-existing simple growth, especially in a papillary cystadenoma but it may arise *de novo*, when it may be solid, or partly cystic from degenerative changes.

In many cases both ovaries are affected, but rarely to the same degree, and it is generally believed that the smaller tumour represents a secondary growth. The tumours rarely attain great size, and may be little larger than hen's eggs. In rare cases they grow rapidly and may assume large proportions. Sometimes they are of firm or even hard consistency, but often they are soft and almost brain-like. Three types of carcinoma may be recognized, according to the microscopic appearances. (1) The common type occurring in a papillary cystadenoma has the structure of a malignant papilloma, and is composed of low columnar or cubical cells arranged in irregular papillary formation. (2) In other cases the structure is that of an adenocarcinoma, and the cells, which show great diversity of form and staining reaction, are arranged around irregular acini. (3) Sometimes the tumour is composed of solid masses of cells, with no acinous arrangement—carcinoma simplex.

Ovarian carcinoma very commonly disseminates through the peritoneal cavity, and secondary growths may be found in all parts, from the diaphragm to the pelvis, leading rapidly to hæmorrhagic ascites. In other cases it disseminates to lymph glands in the iliac and para-aortic group, and to the uterine tubes and areolar tissue of the pelvis.

Secondary Carcinoma of the Ovary

The ovaries show a peculiar liability to attack by malignant cells derived from other sources. The stomach and colon are the common sites of the primary growths, but secondary ovarian deposits may follow cancer of the uterus, gall-bladder or other abdominal organs, and even cancer of distant regions, such as the breast. It is generally acknowledged that the avenue of implantation is through the peritoneal cavity, and it seems that malignant cells set free in the cavity reach the pelvic floor and the ovaries by transcoelomic gravitation.

Secondary growths often affect both ovaries. Usually the nodules are of small size, and are accompanied by metastases in other parts of the peritoneal cavity, but sometimes the ovarian deposits attain considerable size before other secondary growths appear. In such instances they may be mistaken for primary tumours of the ovary,

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particularly if the primary tumour is a symptomless growth of the stomach or colon.

The microscopic appearance depends upon the character of the primary lesion, and this is usually an adenocarcinoma. In some cases the cells undergo "colloid" or mucoid change. They become distended by a clear substance resembling mucin, which displaces the nucleus to one side and gives a characteristic "signet ring" appearance. (Krukenberg tumour.)

Uncommon Tumours of the Ovary

A *Fibroma* of the ovary is somewhat uncommon. It may arise at any age, and grows slowly, forming a firm, solid tumour, which eventually reaches considerable size. Sometimes the growth is en-



FIG. 305. Ovarian metastasis (Krukenberg tumour) from a carcinoma of the colon. The tumour is composed of solid masses of epithelial cells, which are distended to signet-ring shape by intracellular globules of mucin.

(Laboratory of Royal College of Physicians of Edinburgh.)

capsuled, and may be enucleated from the ovary at operation. In other cases it infiltrates the ovary diffusely so that no normal ovarian tissue can be distinguished. A *Fibromyoma* is occasionally found. It resembles the uterine tumour in appearance and behaviour, and is liable to the same kinds of degenerative change. *Endothelioma*, *melanoma*, *rhabdomyoma*, *choriocarcinoma* and other tumours have been observed, but rarely.

Sarcoma of the ovary is rare. It occurs most often at puberty, but has been observed in childhood, and even in the foetus. It is sometimes bilateral. Spindle-cell and round-cell forms have been described. It is usually of great malignancy, and disseminates at an

CYSTS IN THE BROAD LIGAMENT

The broad ligament contains a number of rudimentary structures derived from the Wolffian body and its duct. These structures are known collectively as the parovarium, and they are recognizable in the normal subject when the broad ligament is held up to the light. They consist of a main duct running medially in the base of the broad ligament and a number of short tubules communicating with it. The duct is the rudimentary Wolffian duct, or Gärtner's duct. Laterally it ends blindly; medially it passes down parallel to the vaginal wall and it may open to the exterior in the neighbourhood of the hymen. The tributary tubules are collected in three groups. The ductuli transversi (Kobelt's tubules) lie at the lateral extremity of the broad ligament close to the ovarian fimbria, the tubules of the epoöphoron lie in relation to the

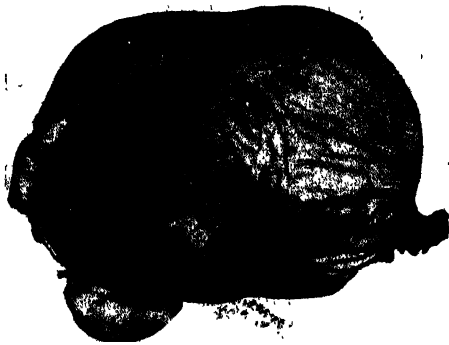


FIG. 306. Cyst of the broad ligament. The Fallopian tube is displaced by the cyst and is incorporated in its wall. The ovary lies below at the left side.

(Department of Midwifery and Gynaecology, University of Edinburgh.)

hilum of the ovary, and the tubules of the paroöphoron are situated more medially.

A cyst may arise from any part of the parovarium. The majority are small pea-like structures arising in Kobelt's tubules at the lateral end of the broad ligament and projecting freely into the peritoneal cavity. It is of little clinical importance. Less often, a parovarian cyst attains the size of a hen's egg, and even greater. It is a smooth, translucent, unilocular structure, which can be readily separated from the peritoneum and enucleated. It consists of a fibrous wall lined by a single row of low columnar ciliated cells, and contains clear, watery fluid of low specific gravity.

Occasionally a cyst in the broad ligament attains great size so that it fills the pelvis and extends upwards into the abdomen. Recent researches suggest that the majority of these cysts arise not at the parovarium but in the displaced ovarian or mesonephric tissues lying in the ovarian fimbria. The uterine tube and fimbria are stretched out over the surface and the ovary is incorporated in the wall, so that it is only distinguished with difficulty. Such a cyst usually resembles true

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parovarian cysts in structure, but sometimes in place of clear fluid it contains pseudomucin. Occasionally intracystic epithelial projections occur, as in papillary cystadenoma.

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